INTRAMOLECULAR [2 + 2] CYCLOADDITION REACTIONS OF ALLENE-YNES: EXPLORING THE SCOPE, MECHANISM, AND APPLICATION TO THE SYNTHESIS OF CARBOCYCLIC SPIROOXINDOLES

by

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INTRAMOLECULAR [2 + 2] CYCLOADDITION REACTIONS OF ALLENE-YNES: EXPLORING THE SCOPE, MECHANISM, AND APPLICATION TO THE SYNTHESIS OF CARBOCYCLIC SPIROOXINDOLES

Joshua M. Osbourn, PhD

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The thermal allene-yne [2 + 2] cycloaddition reaction provides quick and efficient access to alkylidene cyclobutene compounds containing a fused bicyclic ring structure. The mechanism of this reaction was examined computationally in collaboration with Dean Tantillo and Matthew Siebert and experimentally in our lab. Computational studies suggest that the allene-yne [2 + 2] cycloaddition reaction proceeds via a stepwise diradical pathway. It is commonplace for researchers to postulate diradical intermediates for thermally disallowed cycloaddition reactions, but rarely are experiments conducted to support their existence. Experimental efforts to trap the postulated diradical intermediate included appending a cyclopropane to various allene-yne substrates. In two examples, products resulting from cyclopropane ring opening were isolated and characterized, thus providing experimental evidence supporting a diradical intermediate.

The scope of the thermal allene-yne [2 + 2] cycloaddition reaction was expanded to the preparation of spirocyclobutene oxindoles. Our investigation led to the discovery of a tandem thermal [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction of propargyl esters to afford carbocyclic spirooxindoles. This methodology lent itself to the formation of both spirobicyclo[4.2.0]oxindoles and spirobicyclo[5.2.0]oxindoles in moderate yields. The scope of the reaction was expanded to the synthesis of potentially biologically active spirocyclobutene oxindole compounds.

Transfer of chirality from an allene to the [2 + 2] cycloadduct was possible when using a *tert*-butyl substituted allene; however in the case of a propargyl acetate substrate, complete racemization was observed during the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction. We hypothesize that the bulkiness of the *tert*-butyl group and oxindole restricts rotation at the intermediate diradical and thus prevents racemization.

The synthetic utility of the resulting [2 + 2] cycloadducts was briefly examined. The most notable transformations were conversion of the enolacetate of the spirooxindole to the corresponding ketone and α-acetoxyketone.

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The past five years have undoubtedly been some of the most challenging and stressful of my life. There were many times when things got tough and challenges seemed insurmountable. As I faced theses challenges, I would always be reminded of the scripture in Romans 8:28 "And we know that all things work together for good to those who love God, to those who are called according to His purpose." Looking back, as this chapter in my life closes, I know without certainty that every single challenge I faced ended up working out to my benefit and success.

LIST OF ABBREVIATIONS

Ac – acetyl

Bn – benzyl

Boc – *t*-butoxycarbonyl

BTF - benzotrifluoride

Bz – benzoyl

COSY – correlation spectroscopy

Cp - cyclopentyldienyl

DCB – *ortho*-dichlorobenzene

DCE – 1,2-dichloroethane

DIPA – diisopropylamine

DMAP – *N,N*-4-dimethylaminopyridine

DMF – *N,N*-dimethylformamide

DMPU – *N,N*-dimethyl propylene urea

DMSO - dimethylsulfoxide

HMBC – heteronuclear multiple bond correlation

HMQC – heteronuclear multiple quantum coherence

IL – ionic liquid

INT – intermediate

IR – infra-red

LDA – lithium diisopropylamide

LHMDS – lithium bis(trimethylsilyl)amide

MOM - methoxymethyl

Ms – methanesulfonyl

MS – mass spectroscopy

MWI – microwave irradiation

NMP – *N*-methyl-2-pyrrolidinone

NMR – nuclear magnetic resonance

PCC – pyridinium chlorochromate

PR – product

SEM – 2-(trimethylsilyl)ethoxymethyl

SM – starting material

TBAF – tetra-*n*-butylammonium fluoride

TBS – *t*-butyldimethylsilyl

TFA – trifluoroacetic acid

THF – tetrahydrofuran

TLC – thin layer chromatography

TMS – trimethylsilyl

Ts – tosylate

1.0 [2 + 2] CYCLOADDITION REACTION OF ALLENS AND ALKYNES

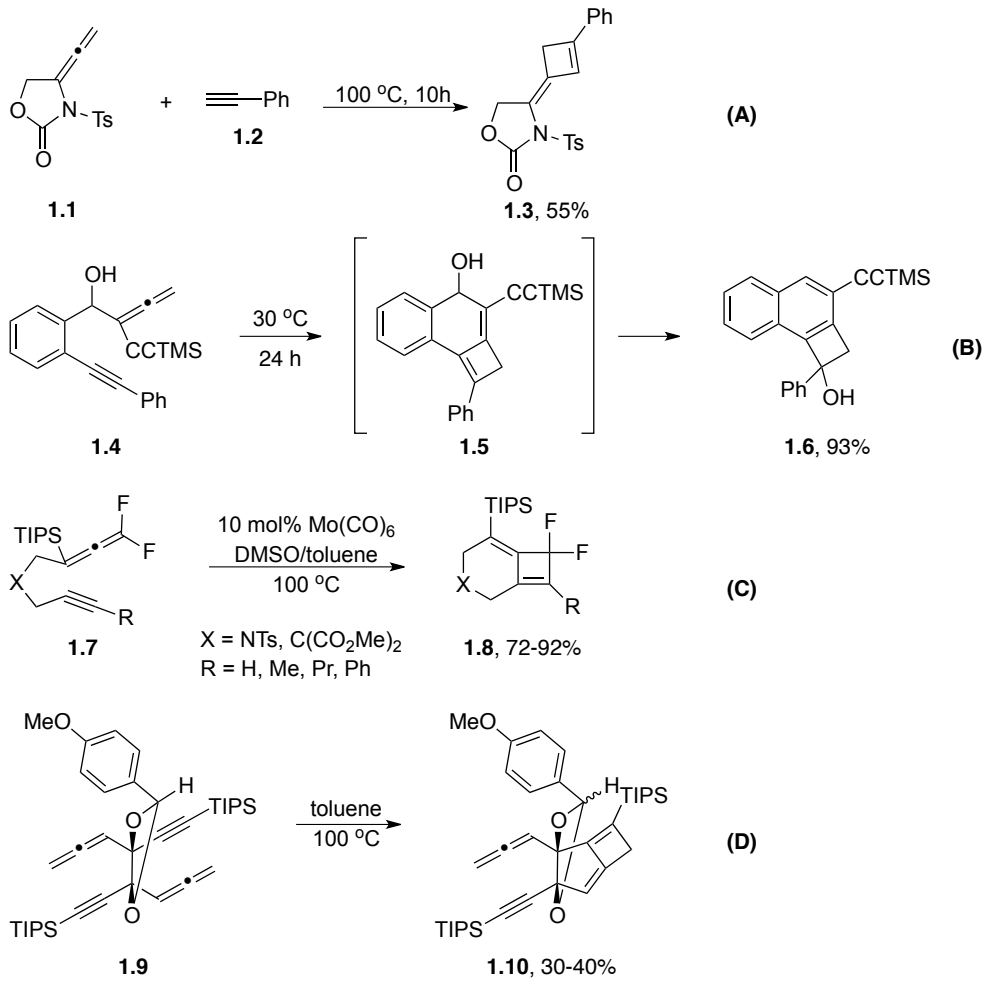
1.1 BACKGROUND AND INTRODUCTION

1.1.1 Pioneering Work in the Thermal Allene-yne [2 + 2] Cycloaddition Reaction

In the field of [2 + 2] cycloaddition chemistry, reactions involving the cycloaddition of alkenes with allenes have been thoroughly studied and many examples have been reported.[1] However, few reports of the cycloaddition between alkynes and allenes have surfaced until recently. The first published example of a [2 + 2] cycloaddition between an allene and alkyne was reported by Roberts in 1956.[2] In this example, phenylacetylene and 1,2-propadiene were heated to 130 ºC in a sealed tube to provide 1-phenyl-3-methylenecyclobutene in a 1% yield.

The first synthetically useful example of a [2 + 2] cycloaddition reaction between an allene and alkyne was reported by Tamaru and coworkers in 1997.[3] Tamaru demonstrated two examples, both of which involve a thermal intermolecular [2 + 2] cycloaddition reaction. By heating oxazolidinone-substituted allene **1.1** with phenyl acetylene (**1.2)** for 10 h, alkylidene cyclobutene **1.3** was produced in 55% yield. This reaction required a large excess of phenyl acetylene (**1.1**) as it was used as the reaction solvent (Scheme 1.1, Eq. A). In 1998, Ueda reported the first intramolecular allene-yne [2 + 2] cycloaddition reaction.[4] While studying the cycloaromatization of ene-diynes, Ueda described three examples in which allene-ynes such as

1.4 were converted cyclobutene fused naphthalenes **1.6**. This reaction was found to proceed via an alkylidene cyclobutene intermediate **1.5**. This intermediate **1.5** was isolated and characterized in one example (Scheme 1.1, Eq. B). Hammond and Cook both independently observed an unexpected intramolecular allene-yne [2 + 2] cycloaddition reaction while studying molybdenum mediated allenic Pauson-Khand reactions. Hammond and coworkers briefly explored the scope of this reaction demonstrating seven examples where difluoro-substituted allenes **1.7** were subjected to the reaction conditions to provide alkylidene cyclobutenes **1.8** with yields ranging from 72-92% (Scheme 1.1, Eq. C).[5] Cook and coworkers reported a single example where allene-yne **1.9** was heated to 100 ºC in toluene to provide alkylidene cyclobutene **1.10** in 30-40% yield (Scheme 1.1, Eq. D).[6] Notably, in the intramolecular examples (Scheme 1.1, Eq. B-D) electrocyclic ring opening of cyclobutene would provide highly strained allene products, which prohibits this normally common transformation.

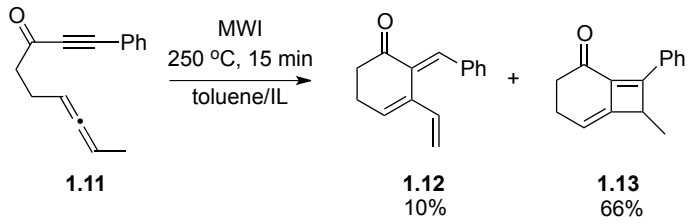


Scheme 1.1 Early Examples (1997-2005) of Synthetically Useful Allene-yne [2 + 2] Cycloaddition Reactions

1.1.2 The First Systematic Study of the Thermal Allene-yne [2 + 2] Cycloaddition Reaction

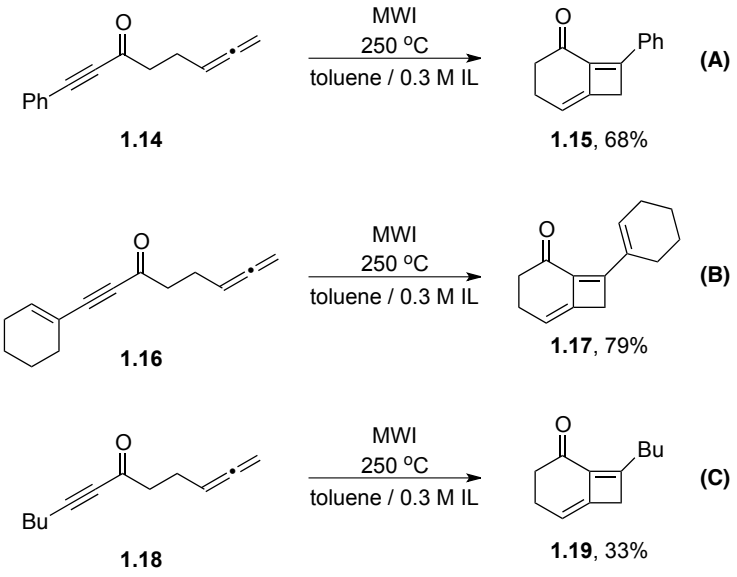
In 2005, while exploring the mechanism of the rhodium catalyzed allenic Alder-ene reaction, Brummond and Chen discovered that upon microwave irradiation of allene-yne **1.11** in toluene doped with ionic liquid at 250 °C, alkylidene cyclobutene **1.13** was formed as the major product in a 66% yield. Triene **1.12** resulting from the allenic Alder-ene reaction was also formed,

however, in only a 10% yield. A requirement for this Alder-ene process is the presence of one or more hydrogen atoms on the carbon substituent at the allene terminus (Scheme 1.2).[7]



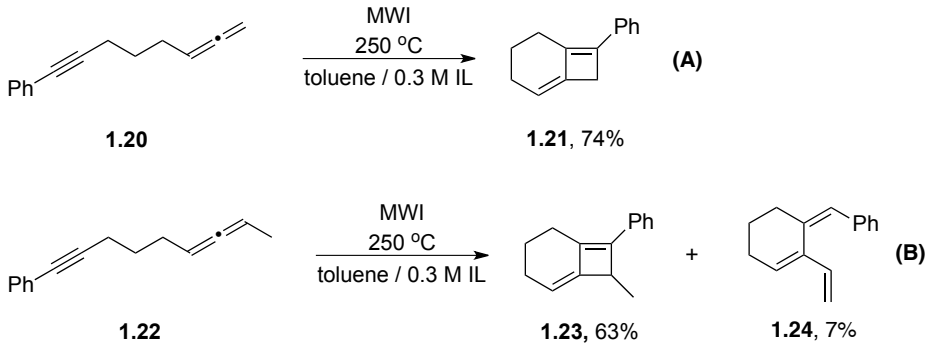
Scheme 1.2 The [2 + 2] Cycloaddition of Allene-ynes by Brummond and Chen

The scope of this allene-yne [2 + 2] cycloaddition was explored by Chen and proved to be rather general. The alkyne substituent was varied to include phenyl **1.14**, cyclohexenyl **1.16**, and butyl group **1.18**. In the case of alkynes substituted with an sp^2-hybridized substituent, the alkylidene cyclobutene products **1.15** and **1.17** were formed in good yields (Scheme 1.3, Eq. A & B). In the case of allene-yne **1.18** containing a butyl group at the alkyne terminus, the yield dropped substantially in the formation of alkylidene cyclobutene **1.19** (Scheme 1.3, Eq. C).



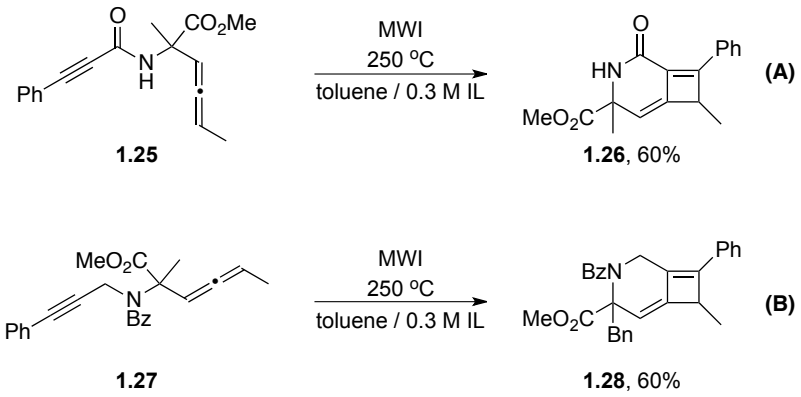
Scheme 1.3 Allene-yne [2 + 2] Cycloaddition: Variations at the Alkyne Substituent

Also examined were substrates **1.20** and **1.22** containing a saturated hydrocarbon tether. Microwave irradiation of allene-yne **1.20** provided alkylidene cyclobutene **1.21** in a 74% yield (Scheme 1.4, Eq. A). In the case of substrate **1.22** containing a methyl group at the alkyne terminus, the alkylidene cyclobutene **1.23** was obtained in a slightly lower 66% yield along with a 7% yield of the Alder-ene byproduct **1.24** (Scheme 1.4, Eq. B). Also of note, substrates similar to **1.20**, but containing a TMS or butyl group on the alkyne terminus resulted in complete recovery of starting material upon subjecting these compounds to the [2 + 2] reaction conditions.



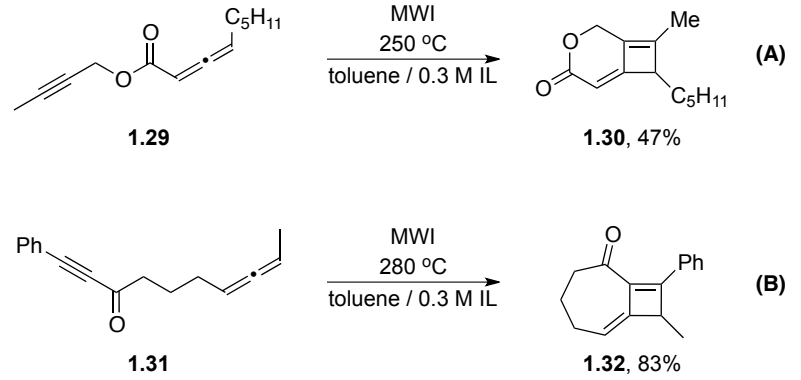
Scheme 1.4 Allene-yne [2 + 2] Cycloaddition: Saturated Hydrocarbon Tether

Next, substrates containing heteroatoms in the tether were examined to investigate their effect on the allene-yne [2 + 2] cycloaddition. Compound **1.25**, containing an unprotected amide in the tether cyclized to provide lactam **1.26** in a 60% yield (Scheme 1.5, Eq. A). When allene-yne **1.27**, containing a benzamide protected amino ester in the tether, was subjected to the reaction conditions alkylidene cyclobutene **1.28** was produced in a 60% yield (Scheme 1.5, Eq. B).



Scheme 1.5 Allene-yne [2 + 2] Cycloaddition: Substrates with Nitrogen in the Tether

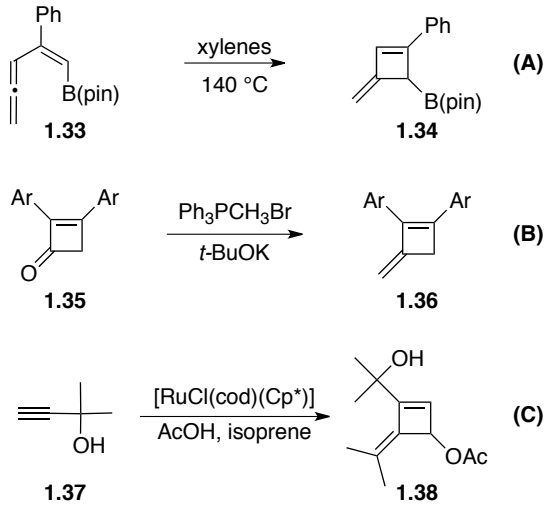
In addition to substrates containing a nitrogen atom in the tether, allene-yne **1.29** containing an oxygen (ester) in the tether was examined. Reaction of **1.29** under microwave conditions provided alkylidene cyclobutene lactone **1.30** in 47% yield. In addition to the [2 + 2] adduct **1.30**, a 28% yield of the cross-conjugated triene byproduct was also formed. This example was not only interesting because of the lactone functionality, but this was one of the few examples where an alkyl group (methyl) is tolerated at the alkyne terminus (Scheme 1.6, Eq. A). In one final example, allene-yne **1.31**, which had its tether length extended by one methylene unit, was subjected to microwave irradiation and provided the [2 + 2] adduct **1.32**, containing a [5.2.0] fused ring system in 83% yield (Scheme 1.6, Eq. B).



Scheme 1.6 Allene-yne [2 + 2] Cycloaddition: Ester Containing and Extended Tether Substrates

1.1.3 Alternative Approaches to Alkylidene Cyclobutenes

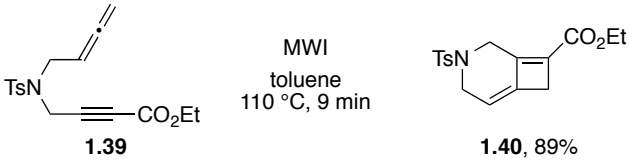
One of the unique features of the thermal allene-yne [2 + 2] cycloaddition demonstrated in our lab is the ability to produce alkylidene cyclobutene products. Alkylidene cyclobutenes are useful in that the double bonds provide a handle for further functionalization allowing for the potential construction of functionalized cyclobutane products. A common approach to alkylidene cyclobutene compounds is via the electrocyclic ring closure of vinyl allenes. This approach is often of limited utility because an equilibrium mixture of starting material and product is produced. Murakami and coworkers demonstrated, however, that by substituting the vinyl alkene of **1.33** with a boron, the reaction equilibrium favored formation of the alkylidene cyclobutene **1.34** (Scheme 1.7, Eq. A).[8] An alternative approach, demonstrated by Semmelhack in 1982, involved formation of cyclobutenone **1.35** via a ketene-alkyne [2 + 2] cycloaddition, and subsequent conversion of the ketone to an alkene under Wittig conditions to provide alkylidene cyclobutene **1.36** (Scheme 1.7, Eq. B).[9] In another approach, Dixneuf showed that by employing ruthenium catalysis, alkylidene cyclobutene **1.38** was afforded via a dimerization reaction involving propargylic alcohol **1.37** (Scheme 1.7, Eq. C).[10]



Scheme 1.7 Methods for the Preparation of Alkylidene Cyclobutenes

1.1.4 Allene-yne [2 + 2] Cycloaddition Reactions Reported Recently

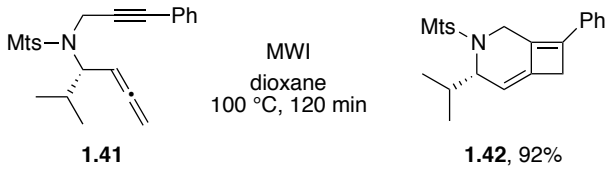
Following the disclosure of the thermal allene-yne [2 + 2] cycloaddition reaction in the Brummond lab, a number of reports involving this interesting reaction surfaced. Almost concurrently with Brummond and Chen, Oh demonstrated the microwave assisted [2 + 2] cycloaddition of allene-ynes in toluene at 110 °C to provide alkylidene cyclobutenes containing a vinyl ester.[11] For example, Oh demonstrated that microwave irradiation of allene-yne **1.39** for 9 min provided the alkylidene cyclobutene **1.40** in an 89% yield (Scheme 1.8).



Scheme 1.8 Allene-yne [2 + 2] Cycloaddition Reported by Oh

Shortly following the report by Oh, Ohno and coworkers demonstrated the first intramolecular allene-yne [2 + 2] cycloaddition reaction of an allene-yne containing a

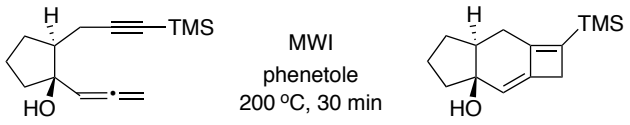
stereogenic center in the molecule. They showed that microwave irradiation of allene-yne **1.41** in dioxane for 2 h at 100 °C provided the alkylidene cyclobutene **1.42** in 92% yield. The stereocenter remained unaffected during the transformation (Scheme 1.9).[12]



1.41 **1.42**, 92%

Scheme 1.9 Allene-yne [2 + 2] Cycloaddition Reported by Ohno

In 2007, Ovaska and Kyne reported a microwave assisted [2 + 2] cycloaddition reaction to provide fused tricyclic products that contain the structural core of the sterpurene family of natural products.[13] Microwave irradiation of allene-yne **1.43** provided the fused tricyclic alkylidene cyclobutene **1.44** in a 90% yield. This transformation was also unique in that it was the first example of a TMS substituted alkyne successfully participating in a thermal allene-yne [2 + 2] cycloaddition reaction (Scheme 1.10).

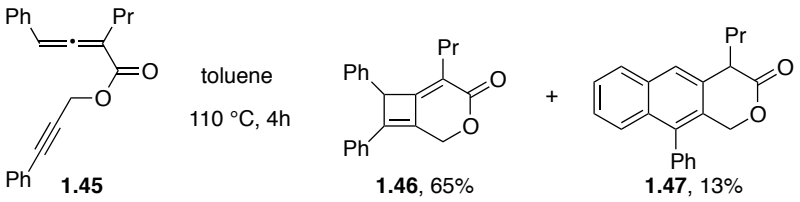


1.43 **1.44**, 90%

Scheme 1.10 Allene-yne [2 + 2] Cycloaddition Reported by Ovaska

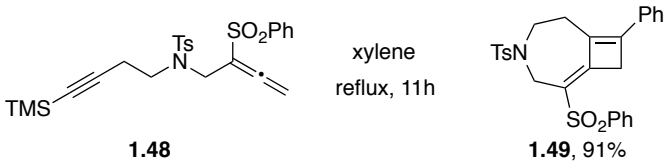
Ma and Jiang demonstrated a thermal (non microwave-assisted) intramolecular [2 + 2] cycloaddition of propargylic 2,3-allenoates as shown in Scheme 1.11.[14] Heating compound **1.45** in refluxing toluene for 4 h provided alkylidene cyclobutene **1.46** in a 65% yield. A corresponding naphthalene product **1.47** was also produced in a 13% yield (Scheme 1.11). Ma also found that the substituent on the allene terminus had a dramatic effect on the reaction rate. Aromatic substitution provided the fastest reaction times (*ca.* 4 h) while aliphatic groups

decreased the rate by nearly a factor of twenty, with reactions taking as long as 72 h to obtain complete consumption of the allene-yne starting material.



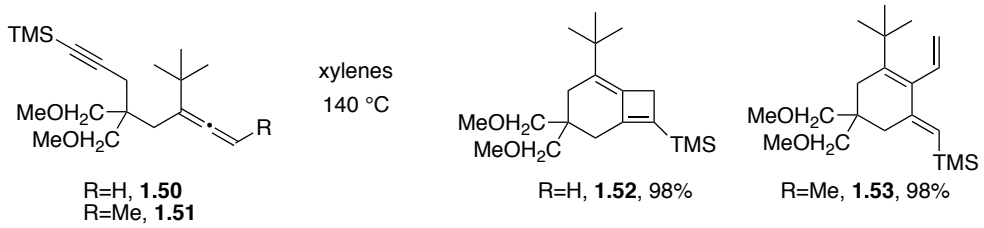
Scheme 1.11 Allene-yne [2 + 2] Cycloaddition Reported by Ma

In 2008, Mukai and coworkers demonstrated the formation of [4.2.0], [5.2.0], and [6.2.0] bicyclic ring systems using the allene-yne [2 + 2] methodology.[15] In their approach, allenyl sulfones where required to attain formation of the alkylidene cyclobutene products in refluxing xylene; no reaction occurred in the absence of the sulfone moiety. Refluxing allene-yne **1.48** in xylene for 11 h furnished the [2 + 2] adduct **1.49** in a 91% yield (Scheme 1.12).



Scheme 1.12 Allene-yne [2 + 2] Cycloaddition Reported by Mukai

One final example, reported in 2008 by Malacria and coworkers demonstrated the allene-yne [2 + 2] cycloaddition of *t*-butylallene **1.50**. Refluxing **1.50** in xylene provided alkylidene cyclobutene **1.52** in a nearly quantitative yield within 12 h.[16] Interestingly, when the terminal allene substituent was changed from a hydrogen to a methyl group **1.51**, the reaction took 96 h to complete and provided only cross conjugated triene **1.53** resulting from an Alder-ene reaction; no [2 + 2] adduct was formed (Scheme 1.13).



Scheme 1.13 Allene-yne [2 + 2] Cycloaddition Reported by Malacria

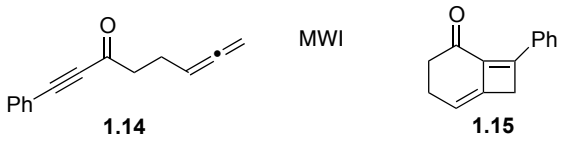
1.2 REEXAMINATION OF THE SOLVENT FOR THE MICROWAVE ASSISTED [2 + 2] CYCLOADDITION REACTION

1.2.1 Introduction

The optimized conditions for the thermal [2 + 2] cycloaddition reaction included microwave irradiation at 250 ºC using toluene containing 0.3 M ionic liquid (1-ethyl-3-methylimidazolium hexafluorophosphate) as the solvent.[7] This protocol involved doping a poorly absorbing solvent (toluene) with one that couples extremely well (ionic liquid) with microwave energy. In this process, microwave energy heats the ionic liquid, which in turn heats the toluene by energy transfer. While the reactions worked well under the conditions described above, we were interested in discontinuing use of ionic liquid for a number of reasons. Most notably, the [2 + 2] cycloaddition reaction of allene-yne **1.20** in the microwave, resulted in one explosion (See Scheme 1.4A). Ionic liquids are known to react with nucleophiles,[17] including alkenes,[18] and it has been suggested that reaction of an alkene with ionic liquid can result in polymerization affording a precipitate that is strongly microwave absorbing.[19] This rapid absorption of microwave energy can lead to explosions. We hypothesize that allene polymerization in the presence of ionic liquid is the cause of microwave explosions experienced in our lab.

Additionally, in the example where an explosion occurred, the substrate was allowed to mature in the ionic liquid/toluene solvent for approximately one hour before the microwave experiment was performed. When the substrate **1.20** was taken up in the reaction solvent and immediately subjected to microwave irradiation, the reaction proceeded smoothly to provide the [2 + 2] adduct **1.21**. A subsequent control experiment was performed where the substrate **1.20** was again allowed to mature in the toluene/ionic liquid solvent for one hour. Microwave irradiation of this mixture once again resulted in an explosion. It should be noted that the explosions described are not the result of a rapid release of pressure, but rather vessel failure due to localized hot spots. Commercial microwave reactors are designed to handle vessel failure safely and without damage to the instrument.

A quest to find an alternative solvent for the [2 + 2] cycloaddition began, and allene-yne **1.14** was chosen as the test substrate. Allene-yne **1.14** was previously shown to undergo the [2 + 2] cycloaddition reaction to provide alkylidene cyclobutene **1.15** using the standard conditions: microwave irradiation for 15 min at 250 ºC in toluene containing 0.3 M 1-ethyl-3-methylimidazolium hexafluorophosphate ionic liquid (Scheme 1.14).[7]



1.14 **1.15**

Scheme 1.14 Substrate Selected for the Microwave Assisted [2 + 2] Solvent Screen

1.2.2 Solvents and Microwave Compatibility

An ideal solvent for the microwave assisted [2 + 2] cycloaddition reaction is one that is high boiling so that it can be heated to high temperatures (150-250 °C) without high pressure (> 20

bar) build-up, yet volatile enough that it can be removed at the end of the reaction under standard reduced pressure. Additionally, the solvent should be unreactive and stable at high temperatures. Finally, the ideal microwave solvent should have a relatively large dielectric constant and relatively small dielectric loss, thus making it an efficient absorber of microwave energy.[20]

1,2-Dichlorobenzene (DCB) is a notable solvent for microwave reactions because it has a large dipole moment (2.50 D) allowing for efficient absorption of microwave energy and a high boiling point (180 °C) allowing for microwave reactions at temperatures up to 250 °C without substantial pressure buildup. One disadvantage to using DCB is difficulty separating the reaction products from the solvent due to its high boiling point. *N,N*-Dimethylformamide (DMF) is also a good solvent for microwave assisted reactions because like DCB it has a large dipole moment (3.82 D) and is an excellent absorber of microwave irradiation. DMF also has a high boiling point (153 °C), allowing it to be heated to high temperatures without considerable pressure buildup. Unlike DCB, DMF can be separated from the products by aqueous washings. Unfortunately, DMF is a reactive solvent under some conditions,[21] and at high temperatures DMF decomposes to carbon monoxide and dimethylamine.[22] DMF is also known to undergo hydrogen atom abstraction under radical conditions,[21] thus potentially interfering with the [2 + 2] cycloaddition reaction, which is hypothesized to proceed via a radical pathway. The solvent *N*-methylpyrrolidinone (NMP) provides the same benefits of DMF, such as the ability to heat to a high temperature and easy removal by an aqueous workup, but NMP does not suffer from decomposition at high temperature like DMF. In addition to DCB, DMF, and NMP, certain lower boiling solvents are candidates for microwave reactions. 1,2-Dichlorethane (bp = 84 °C) and benzotrifluoride (bp = 102 °C) are considered acceptable solvents for microwave reactions because they both have relatively large dipole moments of 2.94 and 2.86 D, respectively. These

solvents are ideal because isolation of the reaction products is easily achieved by concentration under reduced pressure. The only disadvantage to these two solvents is that due to their relatively low boiling points, they can only be heated in the microwave to a maximum temperature of *ca.* 180 °C in most microwave reactors. The ability to heat only to 180 °C is a potential pitfall for the allene-yne [2 + 2] cycloaddition reaction because many substrates require a temperature greater than 200 °C to affect the reaction. In 2011, Anton-Paar introduced a microwave reactor with more than twice the wattage found in competitor models. This additional wattage allows benzotrifluoride and DCE to be heated up to 225 °C under microwave irradiation.

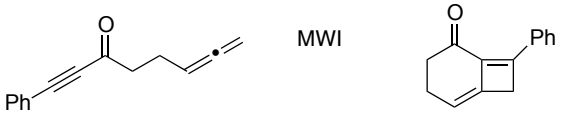
1.2.3 Solvent Study in the Microwave Assisted [2 + 2] Cycloaddition Reaction

Allene-yne **1.14** was irradiated in the microwave for 5, 15 or 50 minutes, depending on the solvent and temperature, to produce cycloadduct **1.15**. The results of this solvent screen are summarized in Table 1.1. When using toluene doped with ionic liquid, the reaction was easily heated to 250 ºC to produce cycloadduct **1.15** in 68% yield in only 15 min (Entry 1, Table 1.1). However, as stated above, we desired to avoid using ionic liquid for safety reasons. Next, using DCB (bp = 180 ºC), the reaction was irradiated at 225 ºC, but the DCB was difficult to remove *in vacuo* (2.5 mm Hg), thus cycloadduct **1.15** was afforded in a rather low, 39% yield (Entry 2, Table 1.1). The low yield is attributed to silica gel column purifications in order to remove the DCB. Next, DMF (bp = 153 ºC) was used as the solvent and the reaction was irradiated at 225 ºC for 15 min. DMF was easily separated from the product by dilution with ether and washing with water. Under these conditions, cycloadduct **1.15** was isolated in 71% yield (Entry 3, Table 1.1). Finally, the more volatile solvents benzotrifluoride (bp = 84 ºC) and 1,2-dichloroethane (DCE, bp = 102 ºC) were examined. These two solvents can be heated to a maximum of 180 ºC

in the microwave before extensive pressure develops and/or the microwave reaches its maximum wattage and cannot further heat the sample. The reaction in benzotrifluoride produced cycloadduct **1.15** in a 58% yield at 180 ºC (Entry 4, Table 1.1), but due to the lower reaction temperature, a longer reaction time (50 min) was required. Similarly, DCE afforded the cycloadduct **1.15** in 84% yield in 50 min at 180 ºC (Entry 5, Table 1.1).

The reaction to form cycloadduct **1.15** is an intramolecular cycloaddition; therefore, the effect of varying the reaction concentration was investigated. The [2 + 2] cycloaddition of **1.14** to provide **1.15** was successfully performed at concentrations of 0.05 M, 0.1 M, and 0.5 M in DCE. The yield at all concentrations screened was *ca*. 85%, and no products resulting from intermolecular reactions were observed by ^{1}H NMR (Entries 5-7, Table 1.1). The reaction was attempted at a concentration of 1.0 M, but the desired reaction temperature of 180 °C could not be achieved. This is likely due the fact that there was not a sufficient amount of solvent/substrate present to efficiently couple with the microwave energy.

Table 1.1 Solvents Screened in the Microwave Assisted [2 + 2] Reaction



1.14 **1.15**

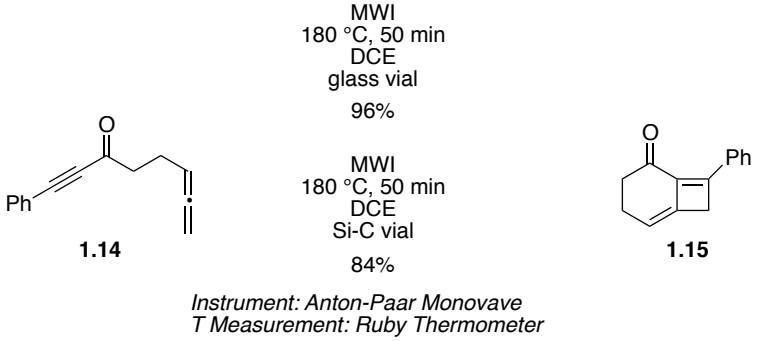
Entry	Solvent/Conc.	Reaction Temperature	Reaction Time	Yield
1	Toluene/0.3 M IL	250 ºC	15 min	68%
2	1,2-Dichlorobenzene (0.05 M)	225 ºC	15 min	39%
3	*N,N*-Dimethylformamide (0.05 M)	225 ºC	15 min	71%
4	Benzotrifluoride (0.05 M)	180 ºC	50 min	58%
5	1,2-Dichloroethane (0.05 M)	180 ºC	50 min	84%
6	1,2-Dichloroethane (0.1 M)	180 ºC	50 min	86%
7	1,2-Dichloroethane (0.5 M)	180 ºC	50 min	86%

In summary, DCE provided the best yield for cycloaddition of allene-yne **1.14** to provide alkylidene cyclobutene **1.15**. However, depending on the substrate, DCB, and DMF have also been shown to be suitable solvents for the allene-yne [2 + 2] cycloaddition reaction when higher reaction temperatures were necessary.

1.2.4 Investigating a "Microwave Effect" In the Allene-yne [2 + 2] Cycloaddition Reaction

An intriguing feature of the intramolecular allene-yne [2 + 2] cycloaddition reaction is that it requires the use of microwave heating to affect conversion to the desired alkylidene cyclobutene products. Conventional heating by refluxing the substrate in a solvent (toluene or xylenes) resulted in no reaction after one day. It is possible that the microwave conditions are only required because the [2 + 2] cycloaddition reaction will not occur at a temperature of less than 180 °C. Heating to 180 °C using conventional methods is often difficult and is avoided due to safety reasons. It is also possible that there is a "microwave effect" involved in the reaction, and that duplication of the conditions under conventional heating would not afford identical results. The microwave effect (non-thermal effect) is a highly controversial topic in the scientific community, and to date has not been proven or disproven.[23] To investigate any non-thermal effects in our microwave assisted allene-yne [2 +2] cycloaddition reaction, the reaction was performed in a silicon carbide vessel using the Anton-Paar Monowave microwave synthesizer. By using a silicon carbide vessel, all microwave energy is directly absorbed by the vial and subsequently transferred to the reaction mixture in the form of heat. No microwaves directly penetrate the vessel and thus do not enter the reaction mixture. The use of a silicon carbide vial

also requires internal temperature monitoring which was carried out using a ruby thermometer attachment. Using identical conditions and an identical method for temperature measurement, allene-yne **1.14** was subjected to the [2 + 2] cycloaddition in both a glass vial and a silicon carbide (Si-C) vial as shown in Scheme 1.4. When the reaction was performed in a glass vial, a 96% yield of alkylidene cyclobutene **1.15** resulted. When the reaction was carried out in a Si-C vial, an 84% yield of **1.15** was obtained. Although the yield of the reaction performed in a Si-C vial is slightly lower, the reaction still proceeded smoothly. Based on this result, it is unlikely that any microwave effect is involved in the thermal allene-yne [2 + 2] cycloaddition; the microwave reactor is merely a tool to achieve high reaction temperatures that are difficult to obtain conventionally (Scheme 1.15).



Scheme 1.15 Microwave Assisted [2 + 2] Cycloaddition of 1.14 in a Glass vs. Silicon Carbide Vial

2.0 THE MECHANISM OF THE THERMAL INTRAMOLECULAR ALLENE-YNE [2 + 2] CYCLOADDITION REACTION

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2.1 INTRODUCTION AND BACKGROUND

The [2 + 2] cycloaddition reaction is a convenient method for the formation of four membered rings. Many of the earliest reports of allenes in natural product synthesis utilize their ability to undergo [2 + 2] cycloaddition reactions.[24] To date, a significant amount of research has focused on the [2 + 2] cycloaddition between *alkenes* and allenes; however, until recently the [2 + 2] cycloaddition reactions between *alkynes* and allenes has remained quite elusive.

In 2005, our group reported the first systematic study of the thermal allene-yne [2 + 2] cycloaddition reaction.[7] In this report, the reaction was shown to be quite versatile allowing a variety of substitution on the alkyne, on the allene, and in the tether, providing both [5.2.0] and [4.2.0] cycloadducts in good yields. Following this report, a number of other groups have shown similar reactivities of allene-ynes under a variety of reaction conditions.[11-16]

The mechanism of thermal [2 + 2] cycloaddition reaction has frequently been of interest because this suprafacial process is symmetry forbidden based on the Woodward-Hoffman

rules.[25] In many cases, there is strong evidence pointing to biradical or ionic intermediates in these processes.[26] Literature concerning the mechanism of the [2 + 2] cycloaddition of allenes and alkynes is quite scarce. In 1992, Pasto studied the cycloaddition reaction of enantioenriched allenes with methyl propiolate.[27] In this example, two cycloadducts were formed with a 40% transfer of enantiomeric excess. *Ab initio* calculations were also performed and indicated formation of an anti,syn biradical.

Herein we describe our efforts to explore the mechanism of the allene-yne [2 + 2] cycloaddition reaction using experimental methods performed in our lab, as well as computational methods performed by Dean Tantillo and Matthew Siebert (U.C. Davis). Understanding the mechanism of this cycloaddition reaction will allow us to better predict substrates that will successfully participate in the reaction, as well as provide information as to which factors might accelerate or slow the reaction. Furthermore, mechanistic information and the understanding of reaction intermediates might allow us to design novel reactions that exploit these intermediates to build exciting new chemical scaffolds.

2.1.1 Orbital Symmetry in the [2 + 2] Cycloaddition Reaction

Thermal [2 + 2] cycloaddition reactions are intriguing because they are forbidden based on the conservation of orbital symmetry rules. Laid out by Woodward and Hoffmann, these rules state that during a concerted process, conservation of orbital symmetry must occur in going from the reactant(s) to the product.[25] For a thermal [2 + 2] cycloaddition to occur with conservation of orbital symmetry, two electrons from the alkene starting material will correspond to an excited state in the cyclobutane product. This is a very high-energy system and is thus considered a forbidden process. In a thermal pericyclic process, the HOMO of one π-system and LUMO of

the other π-system must mix in phase. As shown in Figure 2.1, in the case of a thermal [2 + 2] cycloaddition, the two alkenes cannot mix in phase and thus prohibits this process. The thermally forbidden process is formally termed a [π2s + π2s] cycloaddition where "π" is the type of bonds involved, "2" is the number of electrons, and "s" designates that the two p orbitals of the alkene are suprafacial (orbitals on the same face are involved in mixing).

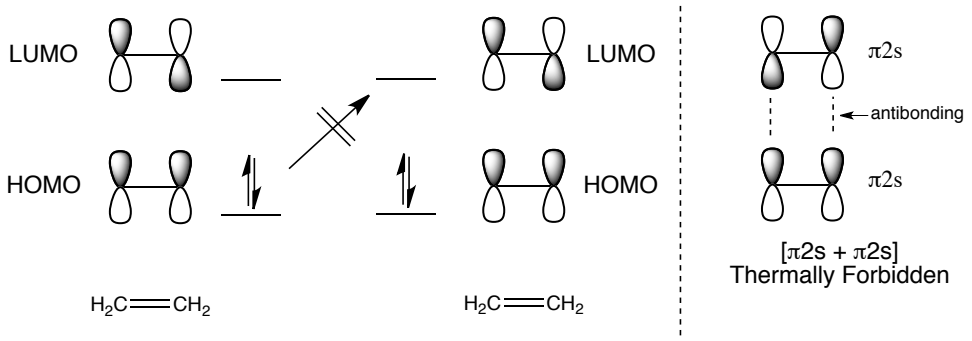


Figure 2.1 Thermally Forbidden [2 + 2] Cycloaddition

Most commonly, [2 + 2] cycloadditions are carried out under photochemical conditions. This process is allowed based on the conservation of orbital symmetry. Subjecting an alkene to energy from light promotes one of the electrons to a higher energy level. This electron residing in the SOMO (new HOMO) can now mix with the LUMO of the other alkene in an allowed [π2s + π2s] process (Figure 2.2).

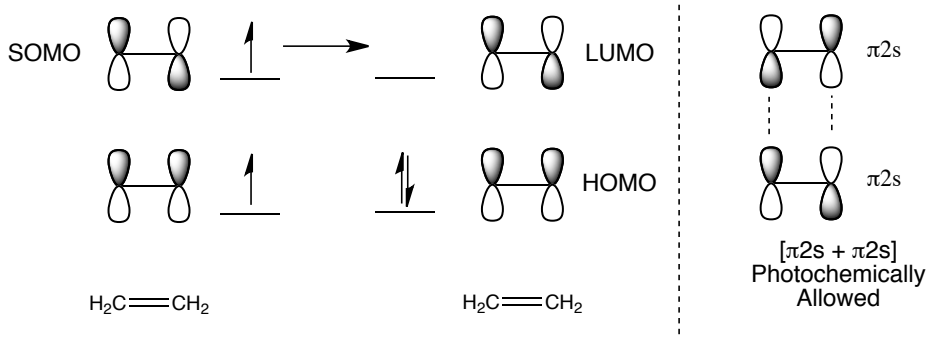


Figure 2.2 Photochemically Allowed [2 + 2] Cycloaddition

Considering the information discussed above, how then can we explain the numerous examples of thermally promoted [2 + 2] cycloaddition reactions in the literature, including the allene-yne [2 + 2] cycloaddition? In many cases, a non-concerted diradical mechanism is invoked; however, certain linear molecules such as ketenes[28] and allenes[29] can undergo a concerted [2 + 2] cycloaddition via a non-pericyclic coarctate reaction.[30] The concerted allene-alkene [2 + 2] reaction involves mixing orthogonal allene p-orbitals with suprafacial alkene p-orbitals. By invoking the orthogonal p-orbital of the allene, the cyclic nature of the transition state, as observed in pericyclic reactions, is broken, thus making this a coarctate process. Figure 2.3A shows mixing of the alkene HOMO orbitals with perpendicular allene LUMO orbitals. The alternative process, shown in Figure 2.3B, involves mixing two parallel antarafacial allene HOMO orbitals with two suprafacial alkene LUMO orbitals. While this process is thermally "allowed," it is generally considered unlikely because the steric interactions are too great (Figure 2.3).

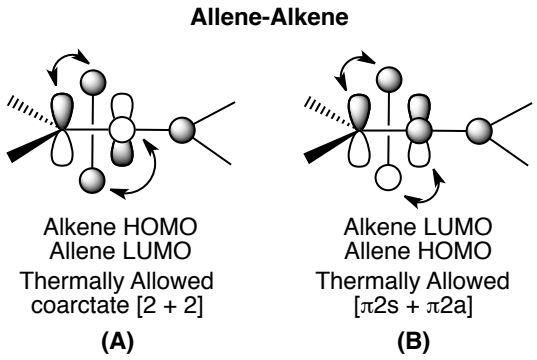
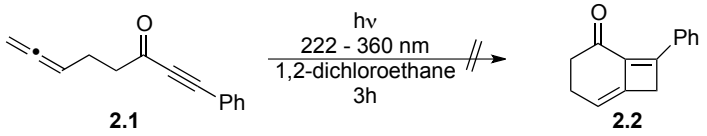


Figure 2.3 Thermally Allowed Suprafacial/Antarafacial [2 + 2] Cycloaddition

2.2 EXAMINING THE POSSIBILITY OF A PHOTOCHEMICALLY ACTIVATED [2 + 2] CYCLOADDITION

While the thermal [$\pi 2_s + \pi 2_s$] cycloaddition reactions are forbidden by orbital symmetry rules, the photochemical reactions are quite common. During the microwave assisted [2 + 2] cycloaddition reactions performed in our lab, no precautions were taken to ensure light was not entering the reaction vessel. We were therefore interested to see if the allene-yne [2 + 2] cycloaddition reaction could be occurring under photochemical initiation.

To begin, a UV-Vis spectrum of allene-yne **2.1** was obtained to determine the appropriate frequency to promote an electron to the excited state. It was determined that **2.1** absorbs at 280 nm. Next, allene-yne **2.1** was subjected to light emitting between 222 and 360 nm for 3 hours in a quartz reaction vessel. After the reaction, no new products were formed and the starting material **2.1** was recovered completely. Based upon this experiment, the [2 + 2] cycloaddition reaction of allene-ynes is not a photochemically initiated process (Scheme 2.1).

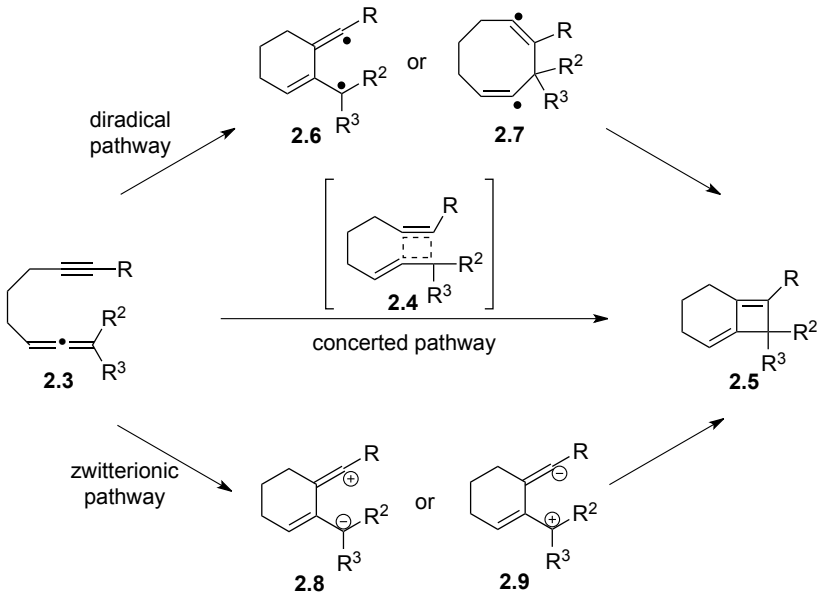


2.1 **2.2**

Scheme 2.1 Subjection of Allene-yne 2.1 to Photochemical Conditions

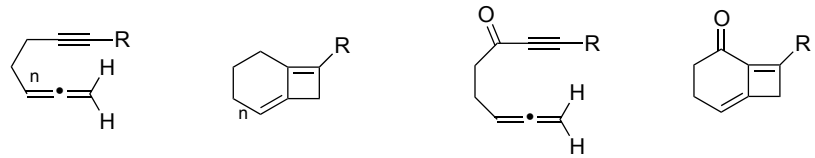
2.3 EXPLORING THE MECHANISM OF THE ALLENE-YNE [2 + 2] CYCLOADDITION REACTION COMPUTATIONALLY: CALCULATIONS PERFORMED BY MATTHEW SIEBERT AND DEAN TANTILLO AT UC DAVIS

Three mechanistic pathways for the allene-yne [2 + 2] cycloaddition reaction were examined: concerted, diradical, and zwitterionic (Scheme 2.2). In the concerted pathway for the transformation of allene-yne **2.3** to cycloadduct **2.5**, a suprafacial / antarafacial approach of the allene and alkyne via intermediate **2.4** is required. For the diradical pathway in the transformation of allene-yne **2.3** to alkylidene cyclobutene **2.5**, a mechanism involving diradical intermediate **2.6** or diradical intermediate **2.7** would be involved. Finally, the zwitterionic pathway could proceed via two different intermediates, **2.8** or **2.9**. For **2.8**, the positive charge exists on the vinyl carbon and the negative charge exists at the allylic position of the cyclohexene. For **2.9**, the negative charge exists at the vinyl carbon and the cation is at the allylic position of the cyclohexene (Scheme 2.2).



Scheme 2.2 Potential Mechanistic Pathways in the Allene-yne [2 + 2] Cycloaddition Reaction

Using B3LYP/6-31+G(d,p) geometry optimization, transition state energy calculations were performed for the [2 + 2] cycloaddition reactions shown in Scheme 2.3. For all substrates examined (**2.10 – 2.16**), there was no indication of a concerted or zwitterionic pathway, but transition states indicating a diradical pathway were discovered.

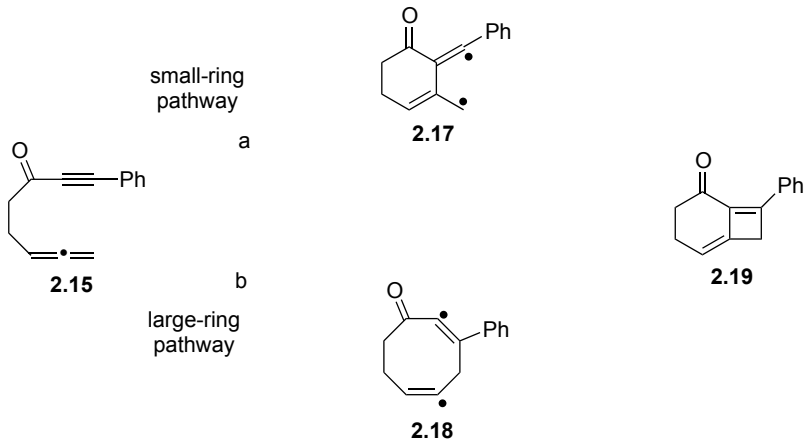


2.10 n = 1, R = H
2.11 n = 2, R = H
2.12 n = 3, R = H
2.13 n = 3, R = Ph

2.14 R = H
2.15 R = Ph
2.16 R = cyclopropyl

Scheme 2.3 Reactions Examined in the Computational Study

Examining the diradical pathway, two routes of ring closure are possible. In the small ring pathway (Path a, Scheme 2.4), initial bond formation occurs to form the six-membered ring **2.17**, followed by subsequent ring closure of the resulting diradical to form the four-membered ring in **2.19**. In the second potential pathway, the large ring pathway (Path b, Scheme 2.4), initial carbon-carbon bond formation gives rise to an eight membered ring **2.18**, containing a diradical. A subsequent carbon-carbon bond formation between the diradical then occurs to provide alkylidene cyclobutene **2.19** containing the [4.2.0] ring system.



Scheme 2.4 Potential Pathways for the Diradical Mechanism

Tantillo and Siebert's calculations found that closure of the small ring first is significantly favored over initial formation of the large ring. As can be seen in the following energy diagrams, (Figures 2.4 and 2.5) the activation energy of the first bond-forming step is 15.1 kcal/mol lower for the small ring pathway than the large ring pathway. This energy difference is rationalized by comparing **2.17** and **2.18**; intermediate **2.17** contains a vinyl radical and a resonance stabilized allylic radical while intermediate **2.18** contains two vinyl radicals with no resonance stabilization.

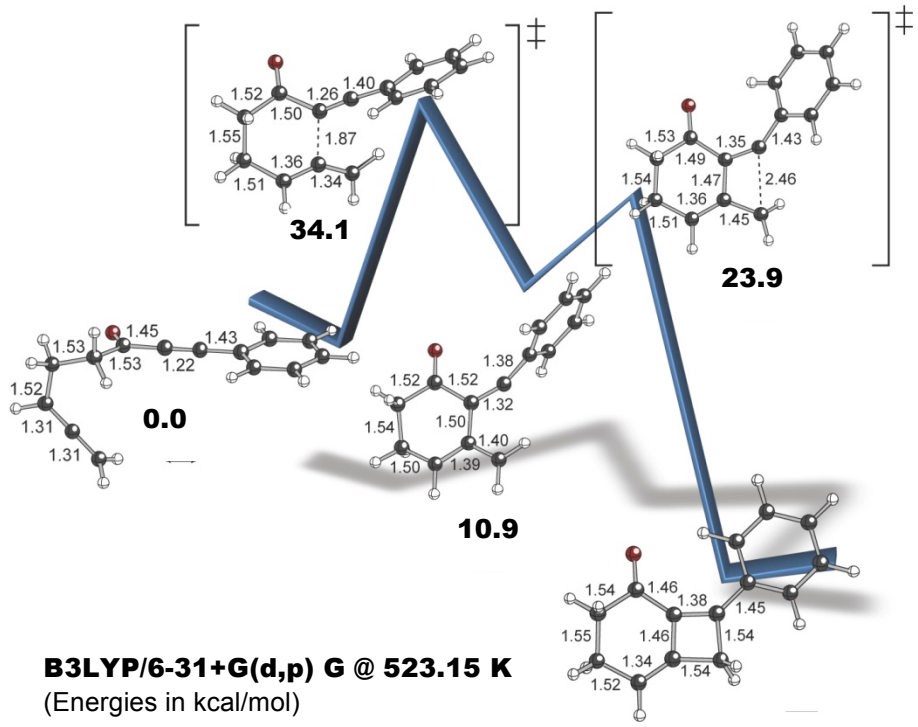


Figure 2.4 Reaction Coordinate: Closure of the Small Ring First

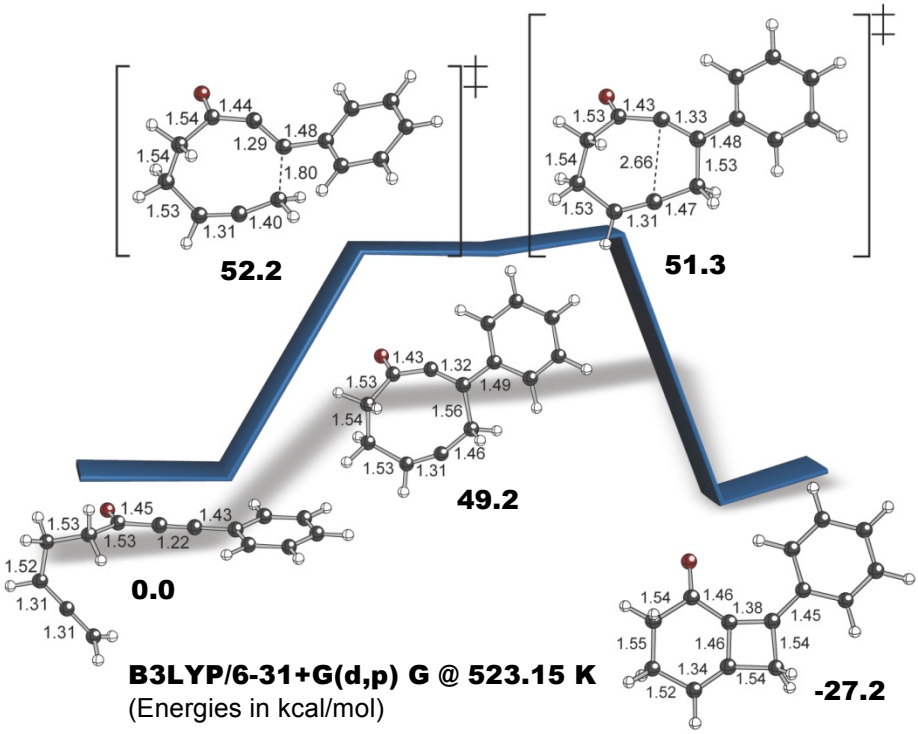
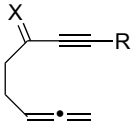
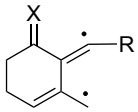
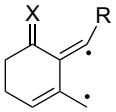
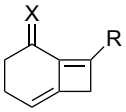


Figure 2.5 Reaction Coordinate: Closure of the Large Ring First

In addition to examining the mechanistic pathway, we were interested in what the computational analysis could tell us about how the various substituents on the allene-yne affect intermediate and transition state energies for the cycloaddition reaction. Understanding the substituent effects will allow us to better design substrates that will successfully participate in the [2 + 2] cycloaddition reaction. The two substituents examined computationally were the carbonyl in the tether and the phenyl group at the alkyne terminus.

Table 2.1 shows the Gibbs free energy calculations at 250 °C for the allene-yne [2 + 2] cycloaddition of substrates containing a phenyl, a carbonyl, a phenyl and carbonyl, and neither a phenyl nor carbonyl substituent. The calculations revealed that the carbonyl had little effect on the reaction energetics with the energies of the transition states and intermediates being lowered by *ca*. 2 kcal/mol when the carbonyl was present (compare entries 1 & 2, Table 2.1). In the system containing the phenyl substituent, more pronounced stabilization was observed. The first transition state (TS1) was lowered by 2 kcal/mol while intermediate 1 (INT1) was *ca*. 6 kcal/mol lower in energy than that observed in the unsubstituted system (compare entries 1 & 3, Table 2.1). In the case of the reaction with the substrate containing both the phenyl and carbonyl there was a modest amount of additional stabilization compared to that with only the phenyl group (compare entries 3 & 4, Table 2.1). When the phenyl substituent is present, there is delocalization of the radical into the phenyl ring. This results in a nearly linear geometry at that site in INT1 and therefore TS2 and INT2 are not observed along the reaction pathway (see entries 3 & 4, Table 2.1).

Table 2.1 Effect of Substituents on the Energetics of the Allene-yne [2 + 2] Cycloaddition[a]

	 SM	TS1	 INT1	TS2	 INT2	TS3	 PR
1	R=H X=H_2	37.5	19.0	22.0	18.4	26.6	-25.7
2	R=H X=O	37.3	17.6	19.8	15.1	25.4	-27.4
3	R=Ph X=H_2	35.4	13.3	-	-	24.4	-23.9
4	R=Ph X=O	34.1	10.9	-	-	23.9	-27.2

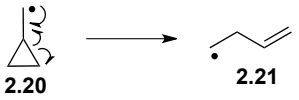
[a]Energy values are reported in kcal/mol and correspond to the Gibbs free energy at 250 °C. The energies are relative to that of the starting material, which is normalized to 0.

The calculations performed by Tantillo and Siebert have provided us substantial insight into the mechanism of the thermal allene-yne [2 + 2] cycloaddition reaction. On the basis of quantum mechanical calculations (B3LYP/6-31+G(d,p)) the reaction is proposed to proceed via a stepwise diradical pathway. In addition to the mechanistic insight, substituent effects were examined and revealed that an aromatic ring on the alkyne terminus lowers the transition state and intermediate energies along the cycloaddition reaction pathway. While it is commonplace for researchers to postulate biradical mechanisms in thermally disfavored cycloaddition reactions, rarely are experiments conducted to provide support for this hypothesis. The computational data discussed above along with experimental data provided in the next section provide unprecedented evidence for this high-energy biradical intermediate in the allene-yne [2 +2] cycloaddition reaction.

2.4 EXPLORING THE MECHANISM OF THE THERMAL ALLENE-YNE [2 + 2] CYCLOADDITION REACTION EXPERIMENTALLY

2.4.1 Introduction

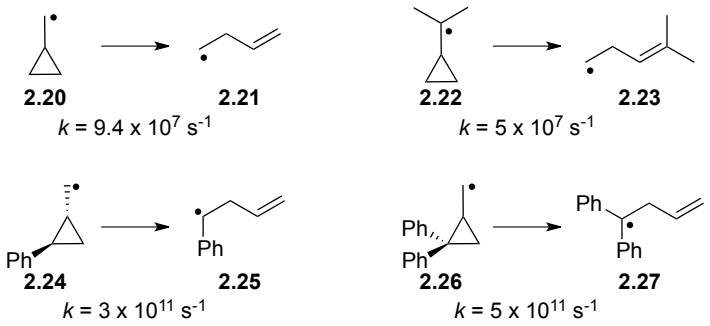
The cyclopropylcarbinyl group has long been used as a radical trap, thus providing evidence for mechanisms involving radical intermediates.[31] The use of this substituent as a radical trap has become so common place that rates of cyclopropane opening have been extensively studied and allow for this group to be used as a radical clock.[32] The use of this substituent as a radical trap requires that the cyclopropyl group be appended to the carbon atom that develops a radical during the course of the reaction. When the radical **2.20** is formed, the cyclopropane opens to give the butenyl radical **2.21**. The driving force for this transformation is release of ring strain in the cyclopropane, as well as formation of a π-bond (Scheme 2.5).



Scheme 2.5 Cyclopropane Opening Due to an Adjacent Radical

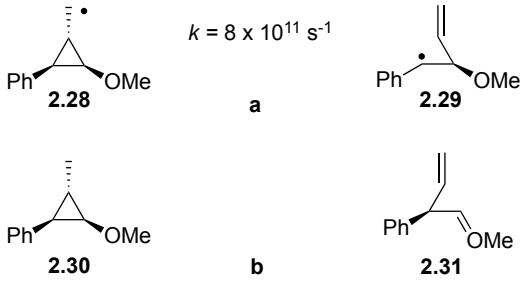
Newcomb has extensively studied radical reaction kinetics and has tabulated the rates of cyclopropane opening for a number of substrates.[32a] An unsubstituted cyclopropane adjacent to a methyl radical **2.20** opens at a rate of 9.4×10^7 s^{-1} to give butenyl radical **2.21**. A more highly substituted radical, such as **2.22**, has additional stability and will open at a slightly slower rate (5×10^7 s^{-1}) to give butenyl radical **2.23**. When a phenyl group is appended to the cyclopropane, as in **2.24**, ring opening due to an adjacent radical will occur at a much faster rate (four orders of

magnitude faster). Finally, when the cyclopropane is substituted with a diphenyl, shown in **2.26**, opening will occur even faster e to produce diphenylbutenyl radical **2.27** (Scheme 2.6).



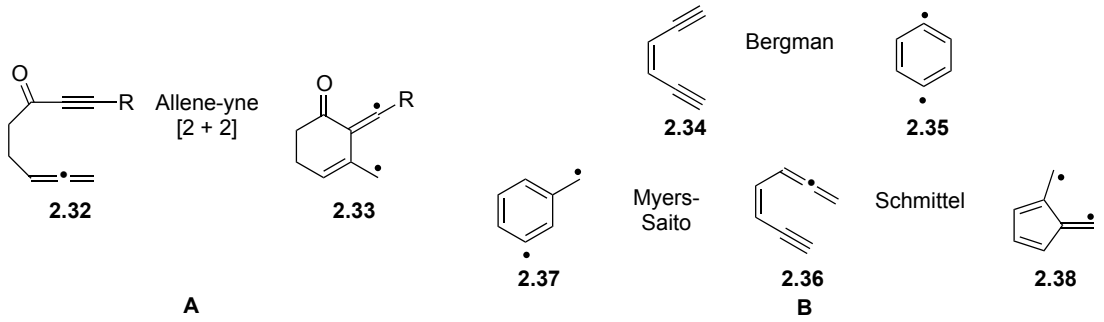
Scheme 2.6 Rates of Ring Opening for Various Cyclopropylcarbinyl Radicals

In addition to the standard cyclopropyl radical clocks, a hypersensitive mechanistic probe for distinguishing between radical and carbocation intermediates has been developed.[33] This probe consists of a cyclopropane that contains both a phenyl substituent and a methoxy substituent. The phenyl group will help stabilize a radical intermediate **2.28**, and will thus promote cyclopropane opening to give a radical trapped product **2.29** (Scheme 2.7a). The methoxy substituent will aid in stabilization of an adjacent carbocation intermediate **2.30**, and can also lead to cyclopropane opening producing **2.31** (Scheme 2.7b). Since opening due to a radical versus opening due to a carbocation results in different products, this probe allows for mechanistic differentiation.



Scheme 2.7 Trapping a Radical or Carbocation Intermediate Using a Single Probe

The most commonly studied radical reactions are those in which the intermediate contains a single radical. In the case of our proposed intermediate **2.33** in the thermal allene-yne [2 + 2] cycloaddition, a diradical is present (Scheme 2.8 A). While there are a number reactions postulated to proceed via a diradical intermediate, only a few have substantial evidence suggesting this mechanism. These include the Bergman cyclization,[34] the Schmittel reaction,[35] and the Myers-Saito reaction (Scheme 2.8 B).[36]



Scheme 2.8 Examples of Diradical Intermediates

Computational predictions suggest that our allene-yne [2 + 2] cycloaddition reaction occurs via a diradical intermediate. To provide additional evidence supporting the presence of a diradical, we wanted to examine the mechanism experimentally. Appending the cyclopropylcarbinyl group to our allene-yne substrate will allow us to probe the mechanism and potentially trap one or more of the intermediates formed during the course of the reaction. Not much is known about trapping diradical species, therefore, we wanted to synthesize a variety of substrates to examine the mechanism. Six allene-yne substrates (**2.39**-**2.44**) were selected to probe the mechanism of the [2 + 2] cycloaddition reaction. The allene-ynes of Series A have the cyclopropane appended to the allene, while the allene-ynes of Series B have the cyclopropane appended to the alkyne (Figure 2.6).

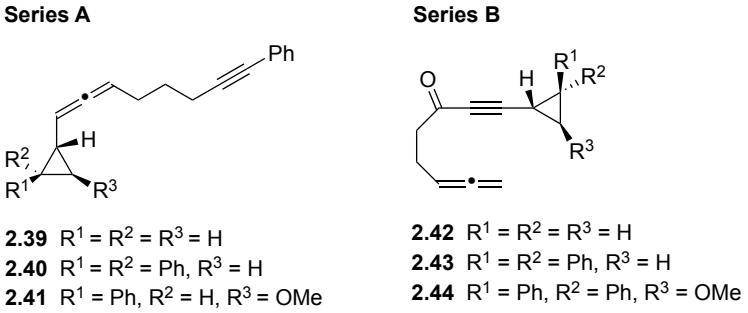
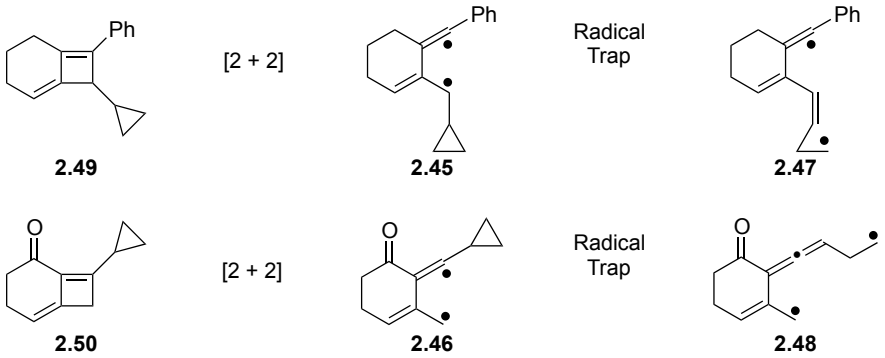


Figure 2.6 Allene-yne Substrates Selected to Probe the Reaction Mechanism

During the course of the reaction, parent cyclopropanes **2.39** and **2.42** should react to give diradical intermediates **2.45** and **2.46**, respectively. Cyclopropane opening will then give rise to intermediates **2.47** and **2.48**. It should be noted that opening of the unsubstituted cyclopropane is reversible, and additionally that ring closure to form the four membered ring may be faster than opening of the cyclopropane ring affording **2.49** and **2.50** (Scheme 2.9).



Scheme 2.9 Cyclopropane Opening vs. [2 + 2] Cycloaddition

If cyclopropane ring opening does not occur using substrates **2.39** and **2.42**, then substrates **2.40** and **2.43** containing the diphenylcyclopropane, and substrates **2.41** and **2.44** containing the methoxyphenyl cyclopropane, may have a fast enough rate of cyclopropane opening to trap the radical intermediate. The unique methoxyphenyl cyclopropane substrates **2.41** and **2.44** will be used to probe the possibility of a zwitterionic mechanism in addition to the diradical mechanism.

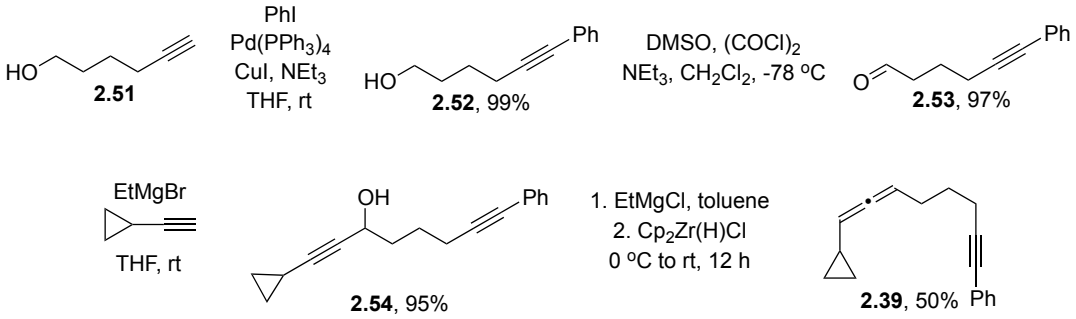
Structurally, the difference in the series A series B substrates (Figure 2.6) lies in the attachment point of the cyclopropane. In series A, the cyclopropane is appended to the allene while in series B, the cyclopropane is appended to the alkyne. Cyclopropane ring opening will provide different products based on its initial attachment point. The reason for the ketone in the substrates contained in series B was merely a synthetic decision, allowing these substrates to be accessed quickly and efficiently. Additionally, as discussed previously, based on computational data, the carbonyl has little effect on the [2 + 2] cycloaddition reaction energetics and thus should have no effect on our mechanistic study.

2.4.2 Preparation of Series A Cyclopropane Substrates

Allene-yne substrates containing the cyclopropyl group appended to the allene terminus (Series A, Figure 2.6) were prepared as described as follows.

Preparation of cyclopropyl allene-yne **2.39** commenced with commercially available 5-hexyn-1-ol (**2.51**), as shown in Scheme 2.10. A Sonogashira coupling between alkyne **2.51** and iodobenzene provided alcohol **2.52** in nearly quantitative yield.[37] The hydroxyl group of **2.52** was oxidized to aldehyde **2.53** in 97% yield via a Swern oxidation.[38] Next, cyclopropylethynyl magnesium bromide was added to aldehyde **2.53** to produce propargyl alcohol **2.54** in 95% yield. Formation of propargyl alcohol **2.54** was confirmed by ^{1}H NMR showing a new resonance at δ 4.4 corresponding to the proton on the carbon containing the alcohol. Four new alkyne resonances at δ 89.7, 88.8, 81.0, and 76.2 and a resonance at δ 62.2 corresponding to the hydroxyl-containing carbon were observed in the ^{13}C NMR spectrum of **2.54**. The IR shows strong hydroxyl and alkyne stretches at 3356 and 2240 cm^{-1}, respectively. The final step of the synthetic sequence was formation of allene **2.39** from propargyl alcohol **2.54**. To affect this

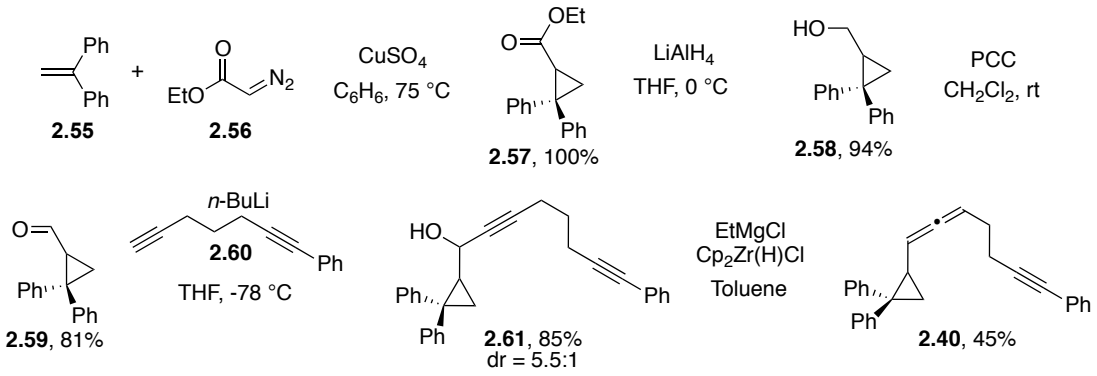
transformation, we performed a two-step, one-pot protocol developed by Pu and Ready in 2007.[39] To a solution of propargyl alcohol **2.54** in toluene at 0 °C was added ethyl magnesium chloride followed by Schwartz's reagent (zirconocene chloride hydride). The allene **2.39** was produced in a 50% yield. Formation of allene **2.39** was confirmed by the disappearance of the propargyl proton resonance at δ 4.4 and the appearance of allene proton resonances at δ 5.21 and δ 5.0 in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **2.39** showed the disappearance of alkyne resonances at δ 76.2 and 88.8, as well as the appearance of allene carbon resonances at δ 203.4, 95.6, and 89.9. The low yield of this transformation can be attributed to a competing reduction of the alkyne in both the starting material **2.54** and the product **2.39** to form styrene derivatives. Both styrenyl byproducts were isolated by column chromatography and characterized by ^{1}H NMR spectroscopy. Furthermore, additional equivalents of Schwartz's reagent did not affect the overall yield of the desired product **2.39** (Scheme 2.10).



Scheme 2.10 Preparation of Allene-yne 2.39

Preparation of diphenylcyclopropyl allene-yne **2.40** began with the copper(II) catalyzed cyclopropanation of 1,1-diphenylethylene (**2.55**) using ethyl diazoacetate (**2.56**) to provide cyclopropyl ester **2.57** in quantitative yield. Lithium aluminum hydride reduction of ester **2.57** to alcohol **2.58** was achieved in 94% yield, followed by reoxidation using PCC providing cyclopropyl aldehyde **2.59** in an 81% yield. The lithium acetylide of diyne **2.60** was added to

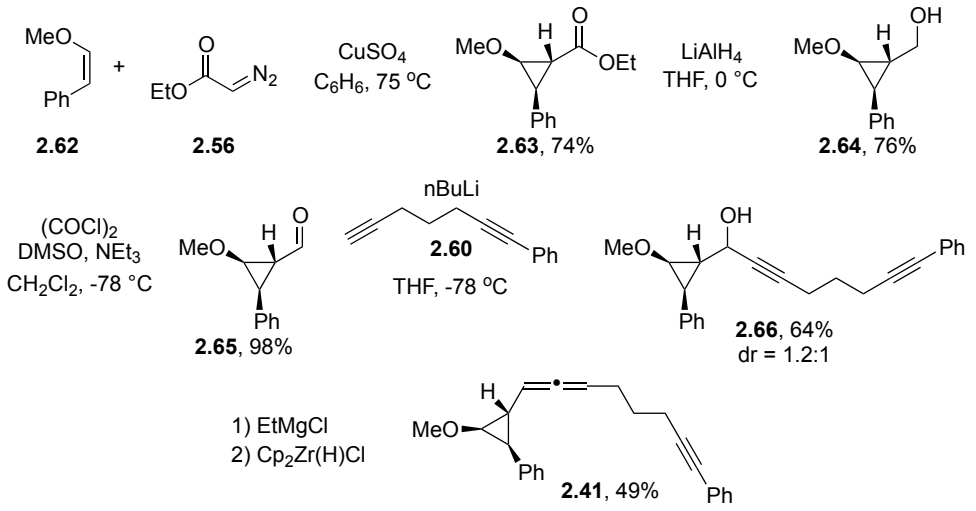
aldehyde **2.59** thus forming propargyl alcohol **2.61** in an 85% yield as a 5.5:1 ratio of diastereomers. Formation of propargyl alcohol **2.61** was confirmed by a key resonance in the ^{1}H NMR spectrum at δ 3.61 corresponding to the propargyl proton adjacent to the alcohol. Finally, using the Ready-Pu allene forming protocol described previously, propargyl alcohol **2.61** was converted to the desired allene **2.40** in 45% yield. Formation of allene **2.40** was confirmed by the disappearance of the propargyl proton resonance at δ 3.61 and the appearance of new allene proton resonances at δ 5.18 and 4.81 in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum of **2.40** also displayed a characteristic resonance at δ 204.6 corresponding to the central allene carbon. Also characteristic was the allene stretch at 1958 cm^{-1} observed in the IR spectrum.



Scheme 2.11 Preparation of Allene-yne 2.40

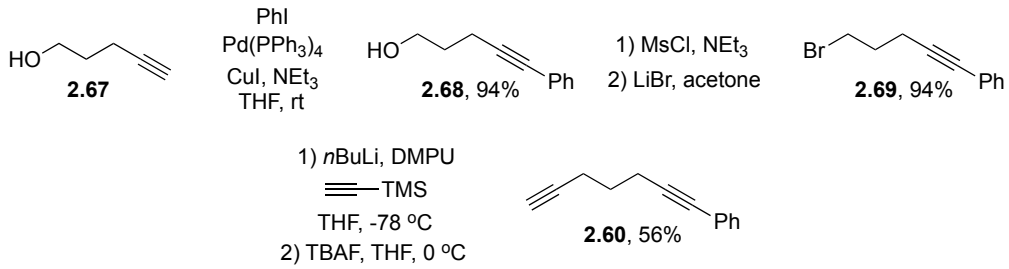
Allene-yne **2.41** was prepared in a manner similar to that of **2.40**. Cyclopropanation of β-methoxystyrene (**2.62**) using ethyl diazoacetate (**2.56**) and copper(II) provided cyclopropyl ester **2.63** as a single diastereomer in 74% yield. Reduction of the ester using lithium aluminum hydride resulted in formation of alcohol **2.64** in 76% yield. The alcohol **2.64** was then oxidized to aldehyde **2.65** in 98% yield via a Swern oxidation.[32a] Addition of the lithiate of diyne **2.60** to aldehyde **2.65** provided propargyl alcohol **2.66** in 64% yield as a 1.2:1 ratio of diastereomers. Finally, allene **2.41** was formed in 49% yield by subjecting propargyl alcohol **2.66** to the Ready-Pu allene forming protocol. Characteristics indicating the formation of **2.41** include the new

allene proton resonances at δ 5.21-5.10 (m) in the ^{1}H NMR spectrum, and the allene stretch at 1958 cm^{-1} in the IR spectrum (Scheme 2.12).



Scheme 2.12 Preparation of Allene-yne 2.41

Diyne **2.60**, used in the preparation of allene-ynes **2.40** and **2.41**, was prepared by a modified procedure of that reported by Yamamoto in 2005.[40] Starting with 4-pentyn-1-ol (**2.67**), a Sonogashira coupling was performed with iodobenzene to produce **2.68** in a 94% yield.[41] Alcohol **2.68** was then converted to a mesylate and immediately displaced by a bromide to provide **2.69** in 94% yield.[42] The bromide of **2.69** was then displaced with lithium trimethylsilylacetylide followed by deprotection of the alkyne with TBAF to produce diyne **2.60** in a 56% yield (Scheme 2.13).

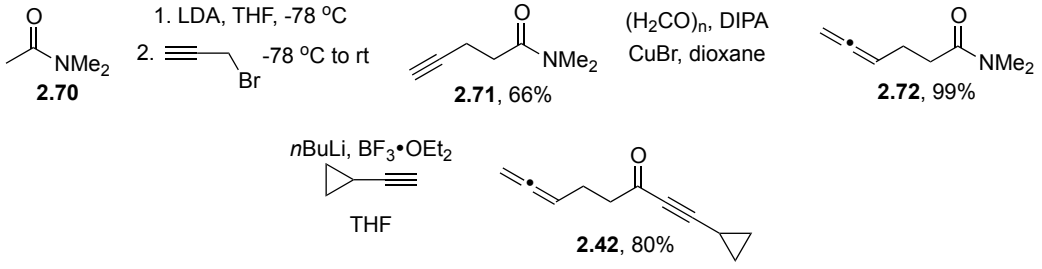


Scheme 2.13 Preparation of Diyne 2.60

2.4.3 Preparation of Series B Cyclopropane Substrates

Allene-yne substrates containing the cyclopropyl group appended to the alkyne terminus (Series B, Figure 2.6) were prepared as described in the following section.

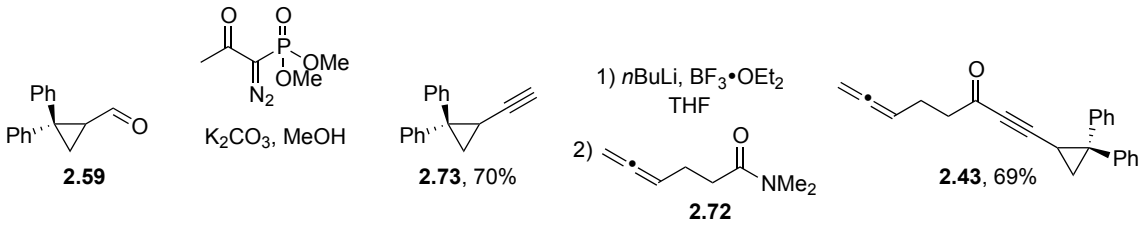
Preparation of allene-ynone **2.42** began with the alkylation of *N,N*-dimethylacetamide (**2.70**) with propargyl bromide to produce ynamide **2.71** in a 66% yield. The alkyne of **2.71** was then transformed to an allene providing **2.72** in nearly quantitative yield via a Crabbé reaction.[43] The two step sequence to prepare compound **2.72** was reported previously in our group.[7] Formation of allene-ynone **2.42** was accomplished in 80% yield by addition of cyclopropyl acetylene to dimethylamide **2.72** using the protocol established by Trost.[44] Formation of **2.42** was confirmed by ^{1}H and ^{13}C NMR spectroscopy. The proximal allene proton resonance appeared as a quintet at δ 5.15 while the distal allene proton resonance appeared at δ 4.71 in the ^{1}H NMR spectrum. The cyclopropyl proton adjacent to the alkyne appeared as a resonance at δ 1.40 in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum of **2.42**, a characteristic central allene carbon resonance appeared at 208.3 ppm (Scheme 2.14).



Scheme 2.14 Preparation of Allene-ynone 2.42

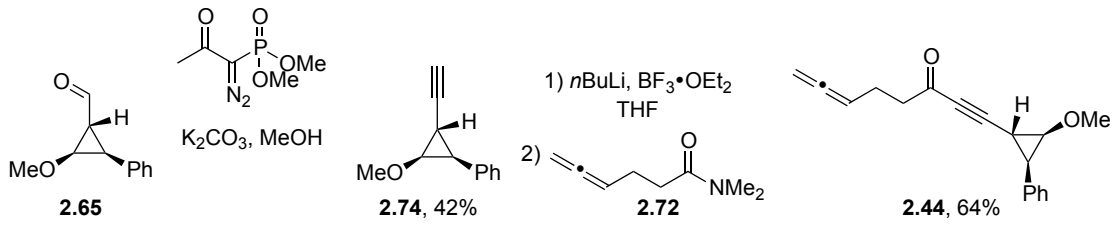
The synthesis of allene-ynone **2.43** commenced by converting cyclopropyl aldehyde **2.59** to cyclopropyl acetylene **2.73** using the Bestmann-Ohira[45] modified version of the Seyferth reaction.[46] Reacting **2.73** with butyllithium resulted in formation of the lithium acetylide, which

was subsequently added to amide **2.72** to provide allene-ynone **2.43** in a 69% yield (Scheme 2.15). Formation of **2.43** was confirmed based on the disappearance of the dimethylamide proton resonances at δ 2.99 and 2.96, and the appearance of new cyclopropane proton resonances at 1.98, 1.91, and 1.80 ppm in the ^{1}H NMR spectrum.



Scheme 2.15 Preparation of Allene-ynone 2.43

Allene-ynone **2.44** was prepared in an analogous manner to that described for **2.43**. Cyclopropyl aldehyde **2.65** was transformed to cyclopropyl acetylene **2.74** in a 42% yield. Formation of the lithiate of acetylene **2.74** and subsequent addition to amide **2.72** provided the desired cyclopropyl allene-ynone **2.44** in a 64% yield. An interesting feature in the ^{1}H NMR spectrum of **2.44** was the relatively far downfield chemical shifts observed for the cyclopropane protons. Most notably, the cyclopropane proton adjacent to the methoxy group appeared as a resonance at 3.79 ppm (dd, J = 3.0, 6.9 Hz) in the ^{1}H NMR spectrum (Scheme 2.16).



Scheme 2.16 Preparation of Allene-ynone 2.44

2.4.4 Mechanistic Investigation using Series A Cyclopropyl Allene-yne Substrates

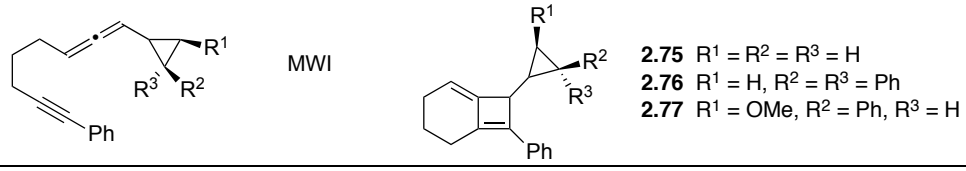
The results of heating the allene-yne substrates from series A are depicted in Table 2.2 and discussed below. The investigation began using parent cyclopropyl allene-yne **2.39**. The substrate was subjected to microwave irradiation for 30 min at 225 °C in 1,2-dichlorobenzene (DCB). Analysis of the reaction mixture showed no products resulting from cyclopropane opening, but complete conversion to the [2 + 2] cycloadduct **2.75** in 83% yield (entry 1, Table 2.2). The key features leading to the identification of cycloadduct **2.75** included the vinyl proton resonance at 5.41 ppm (t, J = 3.9 Hz) and the bis-allylic proton resonance at 3.53 ppm in the ^{1}H NMR spectrum. Due to the instability of cycloadduct **2.75** to column chromatography, an isolated yield could not be obtained. The yield was obtained by performing the reaction in deuterated DCB with 1,4-dimethoxybenzene added as an internal standard. Comparing the integration of the cyclopropane C-H resonance at δ 1.33 in the starting material to the same C-H resonance at δ 1.03 in the product in relation to the internal standard allowed for the NMR based yield determination.

Next, the diphenylcyclopropyl allene-yne substrate **2.40** was subjected to microwave irradiation for 50 min at 180 °C in benzotrifluoride (entry 2, Table 2.2). Analysis of the reaction mixture showed only a trace quantity of the [2 + 2] adduct **2.76**, along with a number of other products inseparable by column chromatography. Separation by HPLC was also unsuccessful. For this example, a lower reaction temperature was necessary due to decomposition observed in a model system when heated to 225 °C (vide infra). In this example, benzotrifluoride was used because it allowed easy isolation of the crude reaction material for the attempted purification.

The final substrate examined from Series A was methoxyphenyl cyclopropyl allene-yne **2.41**. Irradiating this substrate in the microwave for 60 min at 180 °C resulted in the formation of

the [2 + 2] cycloadduct **2.77** in 85% yield (entry 3, Table 2.2). No products resulting from cyclopropane opening were detected. The key resonance in the ^{1}H NMR spectrum indicating the formation of cyclobutene **2.77** corresponded to the bis-allylic cyclobutane proton. This resonance was observed at δ 5.37 for one diastereomers and δ 5.27 for the other.

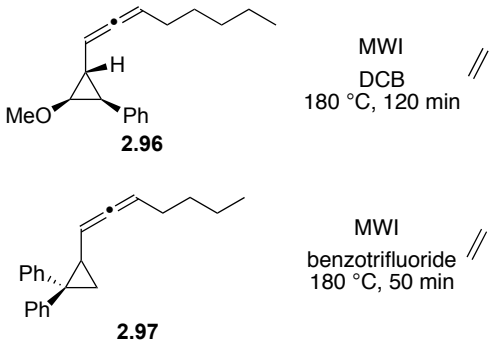
Table 2.2 Results of Heating Series A Allene-yne Substrates



Entry	Substrate	Solvent	T (°C)/time (min)	Yield
1	**2.39**, $R^1 = R^2 = R^3 = H$	DCB-d_4	225/30	**2.75**, 83%
2	**2.40**, $R^1 = H$, $R^2 = R^3 = Ph$	BTF[a]	180/50	**2.76**, trace
3	**2.41**, $R^1 = OMe$, $R^2 = Ph$, $R^3 = H$	DCB	180/60	**2.77**, 85%

[a]BTF corresponds to benzotrifluoride

When irradiating the cyclopropane containing substrates **2.39**, **2.40**, and **2.41** we were concerned that spontaneous cyclopropane opening might occur at the high temperatures required for the [2 + 2] cycloaddition reaction. For each cyclopropane substrate explored, a control substrate containing the cyclopropane appended to the allene, without a tethered alkyne was subjected to the reaction conditions to determine an appropriate reaction temperature that did not cause degradation of the model substrate. In the case of control substrates **2.96** and **2.97**, microwave irradiation at 180 °C provided only recovered starting material. These results indicate that under the reaction conditions, the cyclopropane will not undergo spontaneous ring opening (Scheme 2.17).



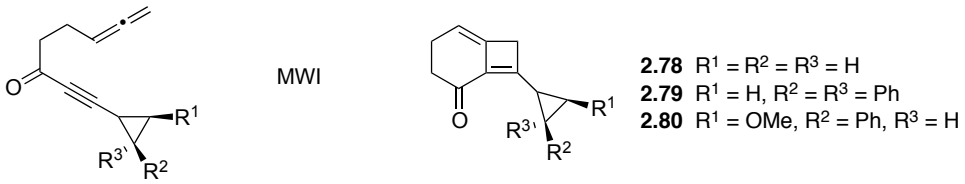
Scheme 2.17 Microwave Control Experiments

2.4.5 Mechanistic Investigation using Series B Cyclopropyl Allene-ynone Substrates

Series B allene-yne substrates (**2.42-2.44**) containing the cyclopropane appended to the alkyne were irradiated under similar conditions as series A allene-ynes, but showed quite different results, which are discussed below.

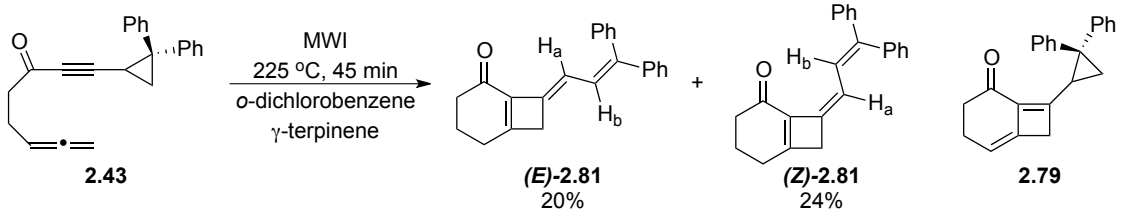
Allene-yne **2.42** containing an unsubstituted cyclopropane group was subjected to microwave irradiation for 30 min at 225 °C in deuterated DCB with 1,4-dimethoxybenzene added as an internal standard. The reaction afforded the [2 + 2] cycloadduct **2.78** in 66% yield based on ^{1}H NMR spectroscopy; no other products were detected in the reaction (entry 1, Table 2.3). A key piece of data that suggested the formation of [2 + 2] adduct **2.78** was the vinyl proton resonance at 5.07 ppm (t, J = 3.6 Hz) in the ^{1}H NMR spectrum. The yield was calculated by comparing the integration of the cyclopropane protons at δ 0.840-0.717 in the starting material and the integration of the same cyclopropane proton protons at δ 0.954-0.937 in the product in relation to the internal standard, 1,4-dimethoxybenzene. While isolation of the product was possible, the product was not stable to silica gel and after purification the yield dropped to 38%. Vinyl cyclopropanes are reported to be readily opened by nucleophilic addition so it is not surprising that isolation of cycloadduct **2.72** was a challenge.[47]

Table 2.3 Results of Heating Series B Allene-yne Substrates



Entry	Substrate	Solvent	T (°C)/time (min)	Yield
1	**2.42**, $R^1 = R^2 = R^3 = H$	DCB-d_4	225/30	**2.78**, 66%
2	**2.43**, $R^1 = H$, $R^2 = R^3 = Ph$	DCB	225/45	**2.79**, 0%
3	**2.44**, $R^1 = OMe$, $R^2 = Ph$, $R^3 = H$	DCB	225/40	**2.80**, 0%

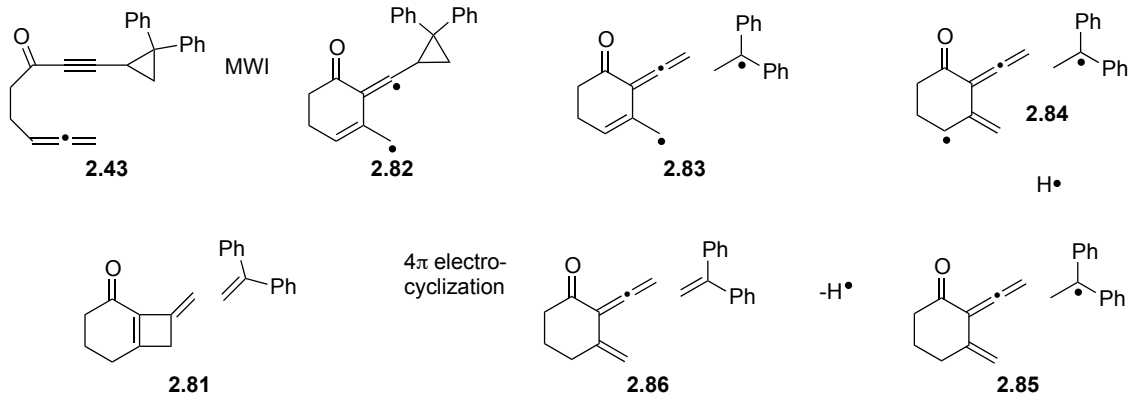
Microwave irradiation of allene-yne **2.43** for 45 min at 225 °C in DCB provided a complex mixture of products. In an effort to simplify the reaction mixture, a hydrogen atom donor, γ-terpinene, was added to the reaction prior to irradiation. The idea behind adding the hydrogen atom donor is that it would potentially quench the diradical species following cyclopropane opening thus leading to less byproducts.[48] Irradiation of diphenylcyclopropyl allene-ynone **2.43** for 45 min at 225 °C in DCB containing γ-terpinene resulted in the formation of two new products identified as the *E* and *Z* isomers of triene **2.81** in 20% and 24% yield, respectively. No [2 + 2] cycloadduct **2.79** was isolated (Scheme 2.18).



Scheme 2.18 Results from Microwave Irradiation of Allene-yne 2.43

The triene products *E* and *Z* **2.81** provide support for a diradical mechanism in the [2 + 2] cycloaddition reaction. A potential mechanism for the formation of the *E* and *Z* isomers of **2.81** is shown in Scheme 2.19. Upon microwave irradiation of allene-yne **2.43**, ring closure occurs to form the six membered ring resulting in diradical **2.82**. The vinyl radical of **2.82** is subsequently trapped by opening of the cyclopropane providing allene **2.83**, a resonance structure of **2.84**.

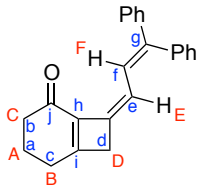
The secondary allylic radical in **2.84** then abstracts a hydrogen atom, presumably from γ-terpinene, to form **2.85**. Next, the diphenyl-substituted radical in **2.85** is quenched by a hydrogen atom abstraction resulting in the formation of **2.86**. The final step is a 4π-electrocyclization between the allene and alkene of **2.86** to provide triene **2.81** as a mixture of *E* and *Z* isomers (Scheme 2.19).



Scheme 2.19 Proposed Mechanism for the Formation of Triene 2.81

Structural elucidation of the *E* and *Z* isomer of **2.85** was achieved using ^{1}H and ^{13}C NMR spectroscopy as well as 2-D COSY and HMQC correlations. The ^{1}H and ^{13}C NMR assignments are listed in Tables 2.4 and 2.5 and the 2-D spectra are provided in Figures 2.7 and 2.8. The COSY spectrum allowed the identification of the $-CH_2^{C}CH_2^{A}CH_2^{B}-$ chain as well as the coupling between alkene protons H_E and H_F. The HMQC spectrum, which allowed for the analysis of $^{1}J_{C\text{-}H}$ coupling, provided the assignments for H_A-H_F. Ten proton signals were assigned to the two phenyl rings and the remaining six carbon (C_m-C_r) atoms were assigned as those not directly coupled to a hydrogen atom. The final carbon atom C_s at 191.3 ppm was assigned as the carbonyl carbon.

Table 2.4 Proton NMR Assignments for (Z)-2.81

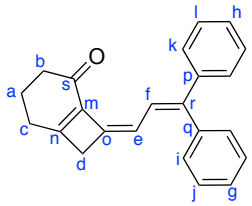


***(Z)*-2.81**

Proton	Chemical Shift (ppm)	Multiplicity	Integration	*J*-Value
A	2.20	quin.	2H	6.3 Hz
B	2.49	t	2H	6.3 Hz
C	2.54	t	2H	5.6 Hz
D	3.16	s	2H	-
E	5.71	d	1H	11.9 Hz
F	7.90	d	1H	11.2 Hz
Ph[a]	7.46-7.43 (m, 4H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.0 Hz, 1H)			

[a]The resonances for the aromatic rings were not unambiguously assigned

Table 2.5 Carbon NMR Assignments for 2.87



***(Z)*-2.81**

Carbon	Chemical Shift (ppm)	Carbon	Chemical Shift (ppm)
a	24.1	g, h	127.1, 127.0
b	25.9	i, j, k, l	127.2, 128.2, 128.3, 130.6
c	38.1	m, n, o, p, q	137.4, 140.1, 140.8, 141.9, 143.5
d	40.1	r	174.9
e	115.2	s	191.3
f	126.8		

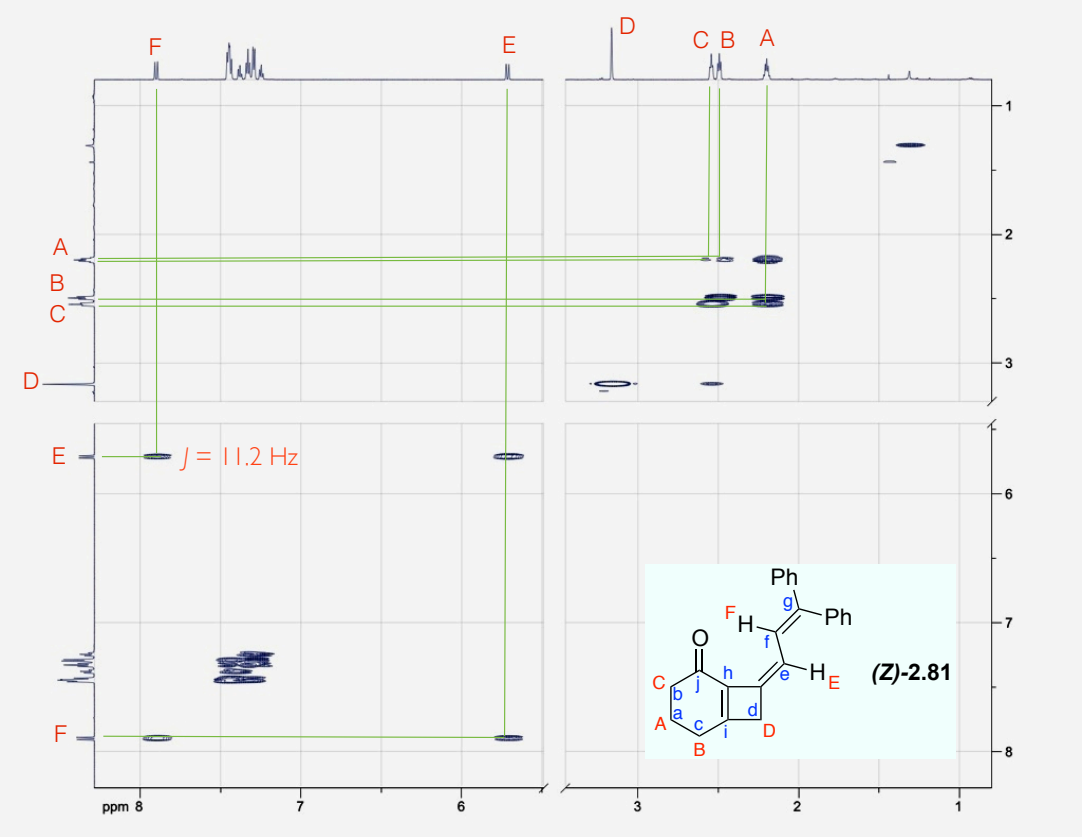


Figure 2.7 COSY Spectrum of *(Z)*-2.81

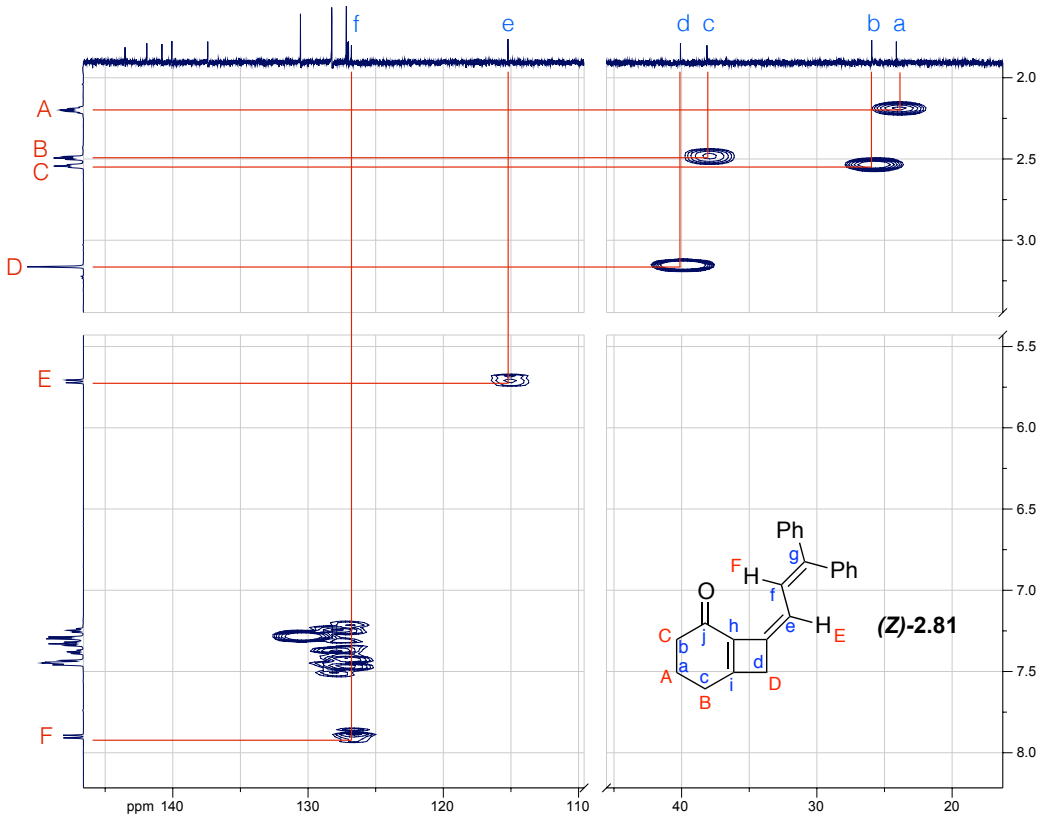


Figure 2.8 HMQC Spectrum for *(Z)*-2.81

One of the more interesting features observed in the ^{1}H NMR spectrum of **2.81** was the chemical shift of the alkene proton resonances of the *E* and *Z* isomers. Not surprisingly, the resonance for H_E in the *E* and *Z* isomers was observed δ 6.64 and 5.71, respectively. For the *E* isomer, H_F appeared as a resonance at δ 6.28. For the *Z* isomer, the resonance for H_F is unusually far downfield at δ 7.9. It is reasoned that this proton was deshielded due to its spatial proximity to the ketone on the cyclohexene ring. To aid in structural confirmation, Spartan calculations (B3LYP) using density functional theory were performed for both the *E* and *Z* isomers of **2.81**. The predicted spectra are nearly identical to those obtained experimentally. Figure 2.9 shows the comparison of the Spartan predicted spectrum of ***(Z)*-2.81** with that obtained experimentally.

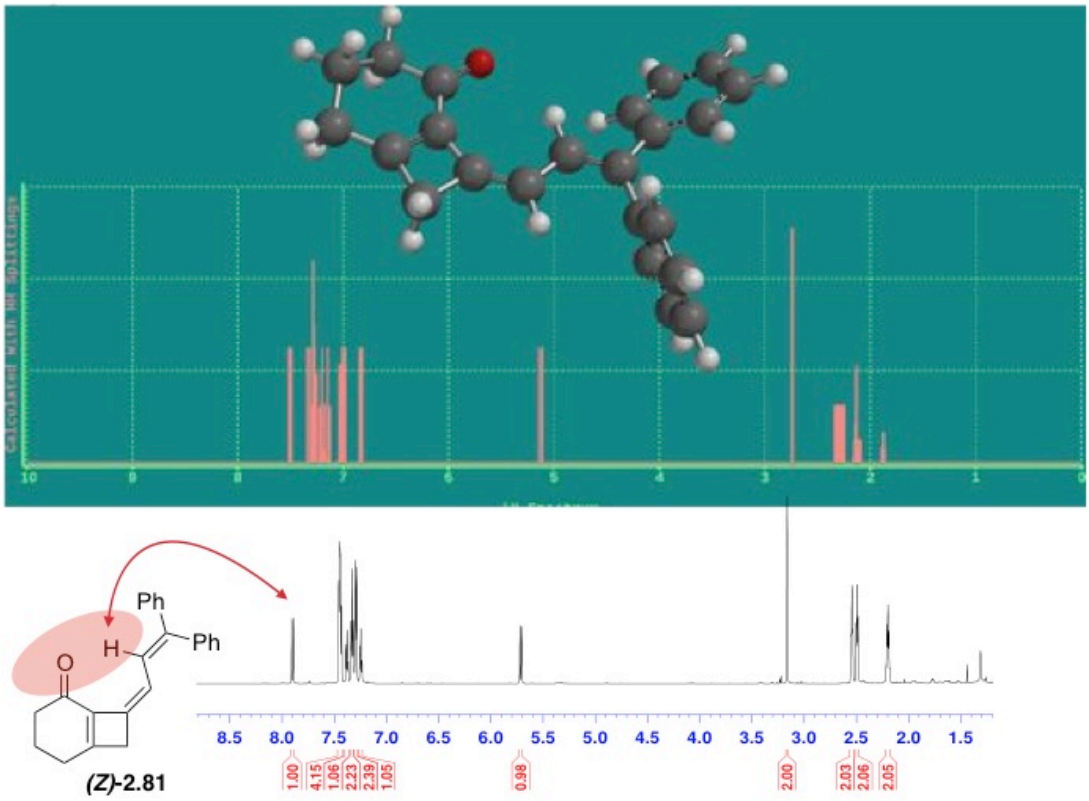
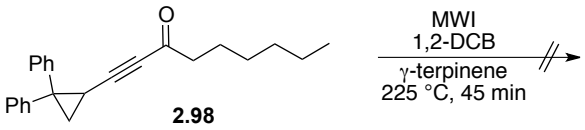


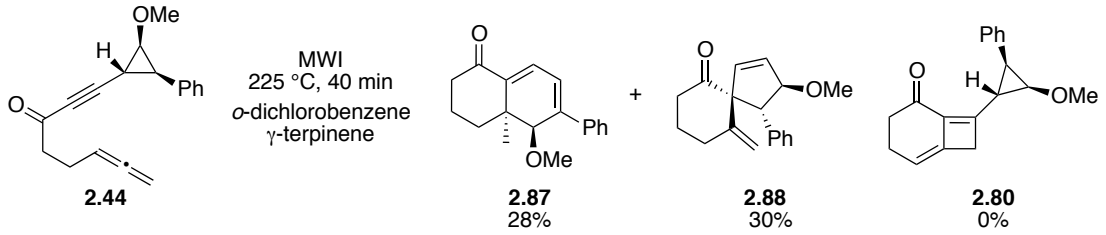
Figure 2.9 Experimental and Predicted ^{1}H NMR Spectrum of *(Z)*-2.81

As in the previous series of substrates, we wanted to ensure the cyclopropane was not spontaneously opening under the reaction conditions. Control substrate **2.98**, containing the diphenylcyclopropane appended to the alkyne, but without the tethered allene was subjected to the reaction conditions (MWI, 225 °C, 45 min). Following the reaction, starting material was completely recovered, thus indicating that the cyclopropane by itself is stable under the reaction conditions (Scheme 2.20).



Scheme 2.20 Microwave Control Experiment

In the final experiment to detect reactive intermediates, the [2 + 2] cycloaddition reaction of allene-ynone **2.44** was examined. This substrate, containing a cyclopropane substituted with both methoxy and phenyl moieties, allows for the interception of both radical and carbocation intermediates. Microwave irradiation of allene-ynone **2.44** for 40 min at 225 °C resulted in the formation of two new products: fused bicycle **2.87** in 28% yield and spirocycle **2.88** in 30% yield. The [2 + 2] cycloaddition product **2.80** was not detected (Scheme 2.21).



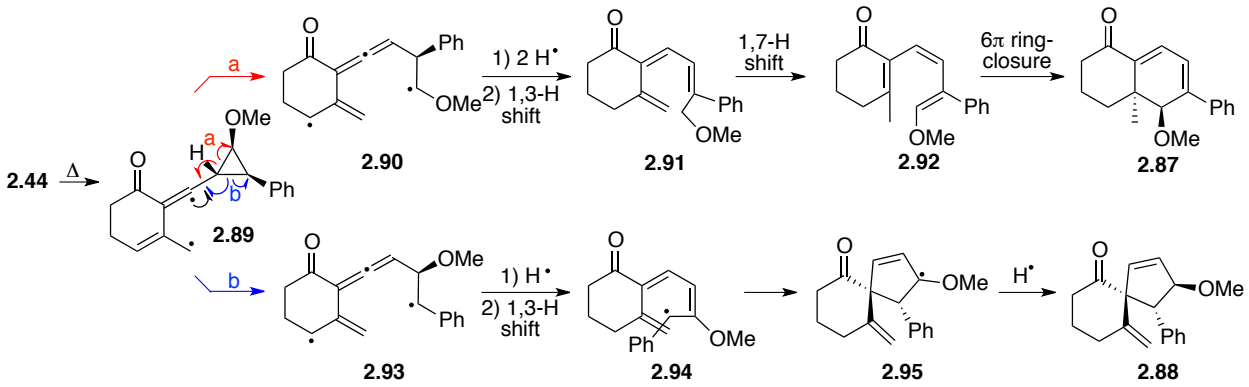
2.44 **2.87** 28% **2.88** 30% **2.80** 0%

Scheme 2.21 Results from Microwave Irradiation of Allene-yne 2.44

The products **2.87** and **2.88** are proposed to be the result of trapping an intermediate diradical. Fused bicyclic diene **2.87** is proposed to arise via path a in Scheme 2.22. Heating allene-yne **2.44** results in bond formation providing diradical intermediate **2.89**. Cyclopropane opening leads to the formation of an allene and methoxy-stabilized radical **2.90**. Diradical **2.90** then abstracts two hydrogen atoms and subsequently undergoes a 1,3-hydrogen atom migration to produce triene **2.91**. Compound **2.91** can then undergo a 1,7-hydrogen atom migration to provide the rearranged triene **2.92**, which can undergo a 6π-electrocyclization to give the product **2.87** (path a, Scheme 2.22).

The proposed formation of spirocycle **2.88** begins with diradical intermediate **2.89**, as in the formation of **2.87**. Cyclopropane opening provides allene **2.93** containing the phenyl-stabilized radical. Next, the allylic radical in **2.93** abstracts a hydrogen atom, followed by 1.3-hydrogen atom migration to provide triene **2.94**. Radical cyclization of **2.94** can occur to

produce spirocycle **2.95**, which can abstract a hydrogen atom to yield the product **2.88** (path b, Scheme 2.22).

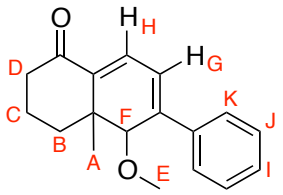


Scheme 2.22 Proposed Mechanism for the Formation of 2.87 and 2.88

Elucidation of the structure of fused bicycle **2.87** was achieved using ^{1}H NMR, ^{13}C NMR, ^{1}H-^{1}H COSY, HMQC, HMBC, IR, and mass spectrometry analysis. The IR spectrum shows a strong ketone stretch at 1671 cm^{-1}. The ^{1}H NMR assignments for **2.87** are listed in Table 2.6. Key resonances observed, include a methyl singlet (H_A, δ 1.14), and a methoxy singlet (H_E, δ 3.22 ppm). Also in the ^{1}H NMR spectrum two coupled alkene protons, H_H and H_G, with a coupling constant of 6.0 Hz were observed; this coupling constant is characteristic for cyclohexadienyl protons. The HMQC (^{1}J C-H coupling) spectrum, shown in Figure 2.10, showed cross peaks for 13 carbon atoms bound to hydrogen. All ^{1}H-^{13}C connectivities were as expected for compound **2.87**. Table 2.7 lists the complete ^{13}C NMR spectral assignments for compound **2.87**. Resonances in the ^{13}C NMR spectrum of **2.87** include the carbonyl carbon at δ 199.4, seven resonances in the aliphatic region (C_a-C_g), and eight resonances in the alkene/aromatic region (C_h-C_o). One of the techniques that aided in complete structural characterization of **2.87** was the HMBC spectrum, which provided proton-carbon coupling spanning 2-3 bonds. The key HMBC correlations are listed in Table 2.8 and the HMBC spectrum is shown in Figure 2.11. As an additional aid in structural confirmation, Spartan 08 was used to predict the ^{1}H NMR spectra of

the various stereoisomers of **2.87**. The predicted spectrum with the stereochemistry as shown in **2.87** matched the actual spectrum closely. Appendix A contains the Spartan predicted spectrum for compound **2.87**.

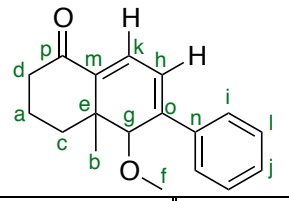
Table 2.6 Proton NMR Assignments for 2.87



2.87

Proton	Chemical Shift (ppm)	Multiplicity	Integration	*J*-Value
A	1.14	s	3H	-
B	1.66-1.69, 2.35-2.41	m, m	1H, 1H	-
C	2.01-2.10	m	2H	-
D	2.35-2.41, 2.63-2.67	m, m	1H, 1H	-
E	3.22	s	3H	-
F	4.06	s	1H	-
G	6.68	d	1H	6.0 Hz
H	7.12	d	1H	6.0 Hz
I	7.38-7.39	m	1H	-
J	7.44	t	2H	7.7 Hz
K	7.61	d	2H	8.4 Hz

Table 2.7 Carbon NMR Assignments for 2.87



2.87

Carbon	Chemical Shift (ppm)	Carbon	Chemical Shift (ppm)
a	17.8	i	126.0
b	22.4	j	128.2
c	29.4	k	128.4
d	39.8	l	128.8
e	40.1	m	139.5
f	57.0	n	140.1
g	81.2	o	140.8
h	122.2	p	199.4

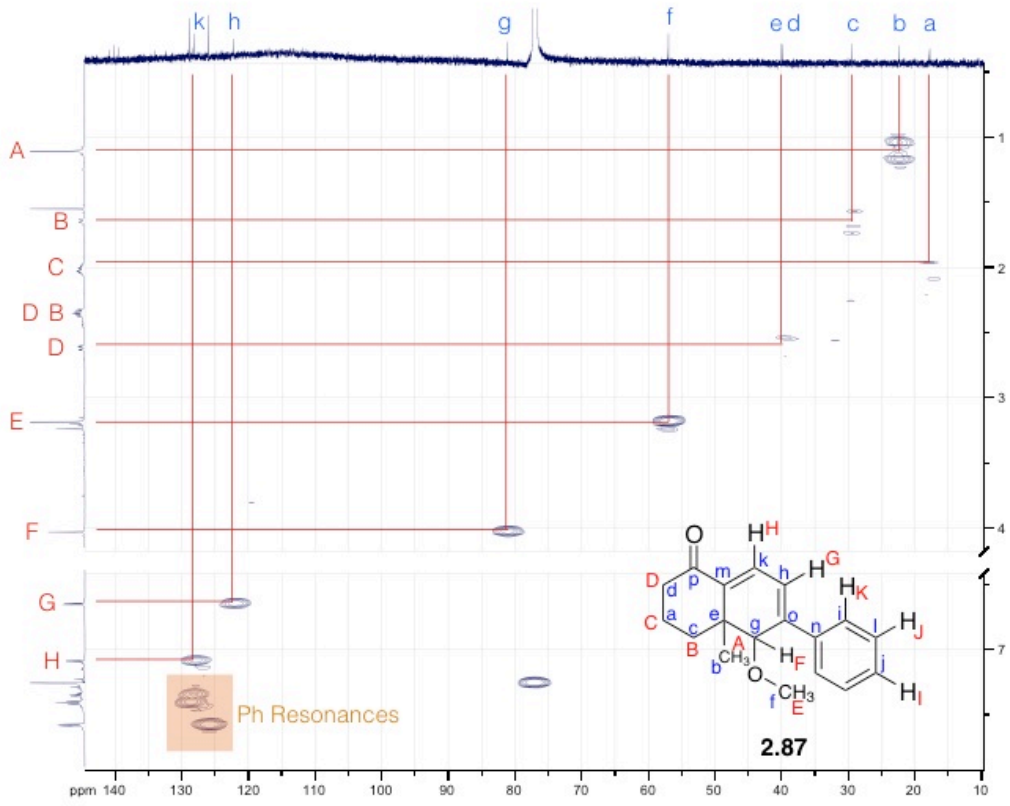


Figure 2.10 HMQC Spectrum of 2.87

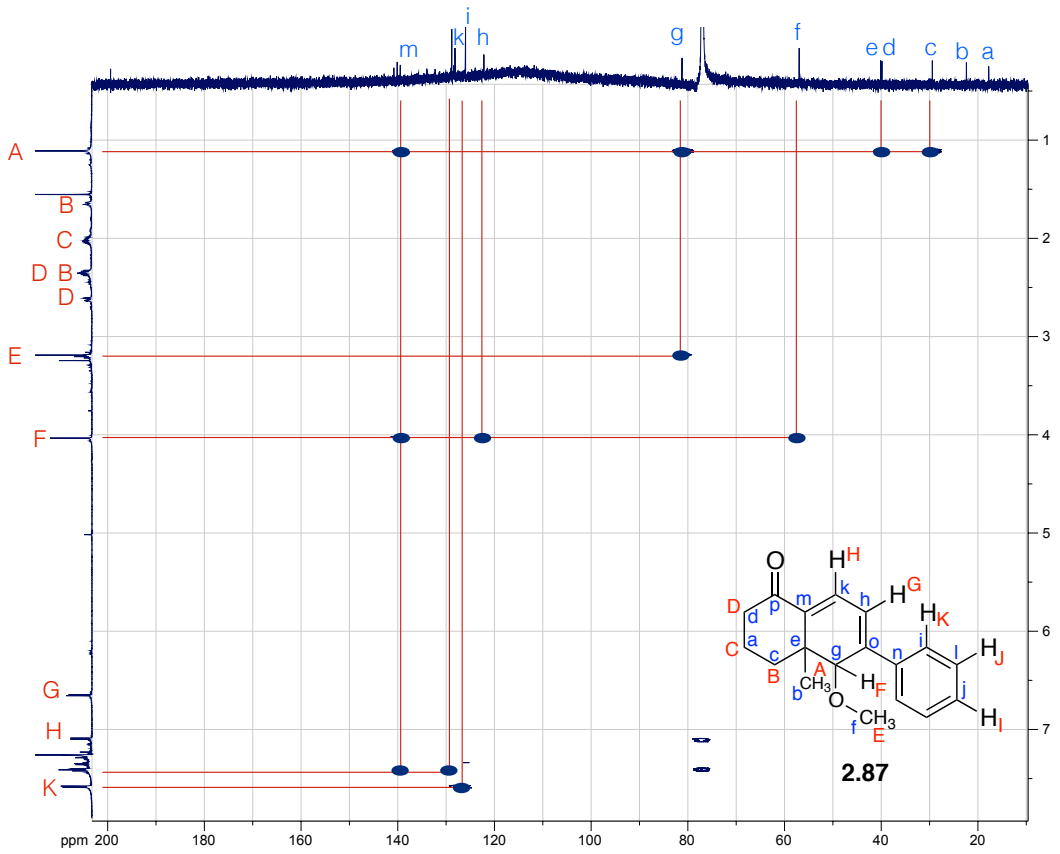
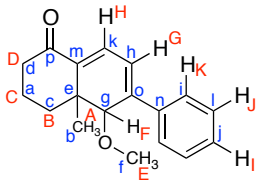


Figure 2.11 HMBC Spectrum of 2.87

Table 2.8 HMBC Correlations for 2.87



2.87

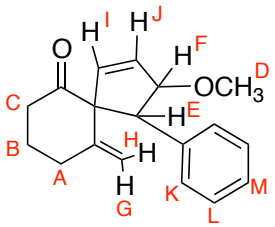
Hydrogens: Upper Case Letters
Carbons: Lower Case Letters

Proton	Observed Coupling With
A	c(^{3}J), e(^{2}J), g(^{3}J), m(^{3}J),
E	g(^{3}J)
F	f(^{3}J), m(^{3}J), h(^{3}J)
H	e(^{3}J), o(^{3}J), p(^{3}J)
K	j(^{3}J)

The structure of spirocycle **2.88** was elucidated using 1D and 2D NMR spectra, IR, and mass spectrometry data. The IR of **2.88** has a characteristic carbonyl stretch at 1707 cm^{-1}. The ^{1}H and ^{13}C NMR assignments (Tables 2.9 and 2.10) were made with the aid of 2-D COSY, HMBC

and HMQC correlations. ^{1}H-^{1}H COSY correlations indicated the coupling of H_B to H_C and H_A. Additionally, H_I and H_J showed a 6.3 Hz coupling typical for olefinic cyclopentene protons. The vicinal protons H_E and H_F had a 5.6 Hz coupling constant. Key resonances in the ^{1}H NMR spectrum of **2.88** included four alkene protons (H_G, H_H, H_I, and H_J), two C-H resonances integrating for 1H (H_E and H_F), and a resonance corresponding to the protons in the methoxy group (H_D). Most of the ^{13}C assignments were revealed based on HMQC ($^{1}J_{C\text{-}H}$) correlations with the exception of C_f, C_n, C_o, and C_p which do not contain an attached proton (Figure 2.12). Assignments for these carbon atoms were made indirectly using longer-range HMBC correlations. Key HMBC correlations included C_o-H_E (^{3}J), C_n-H_E (^{2}J), C_n-H_F (^{3}J), C_f-H_E (^{2}J), C_f-H_G/H_H (^{3}J), and C_f-H_J (^{3}J) allowing for the indirect assignment of these carbons that are not bound to hydrogen (Figure 2.13 and Table 2.11).

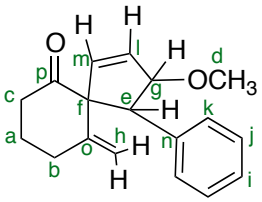
Table 2.9 Proton NMR Assignments for 2.88



2.88

Proton	Chemical Shift (ppm)	Multiplicity	Integration	*J*-Value (Hz)
A	1.05-1.10, 1.99-2.01	m, m	1H, 1H	-
B	1.44-1.51, 1.71-1.75	m, m	1H, 1H	-
C	2.41, 2.49-2.51	ddd, m	1H, 1H	6.3, 13.3, 14.7
D	3.21	s	3H	-
E	3.28	d	1H	5.6
F	4.65	dd	1H	1.4, 5.6
G	4.85	s	1H	-
H	4.92	s	1H	-
I	5.89	dd	1H	1.4, 6.3
J	6.24	dd	1H	1.4, 6.3
K, L, M	7.23-7.31	m	5H	-

Table 2.10 Carbon NMR Assignments for 2.88



2.88

Carbon	Chemical Shift (ppm)	Carbon	Chemical Shift (ppm)
a	23.9	i	127.3
b	32.9	j	128.3 (2C)
c	40.0	k	129.5 (2C)
d	57.1	l	132.5
e	60.0	m	135.7
f	72.4	n	139.7
g	92.1	o	148.4
h	113.8	p	211.4

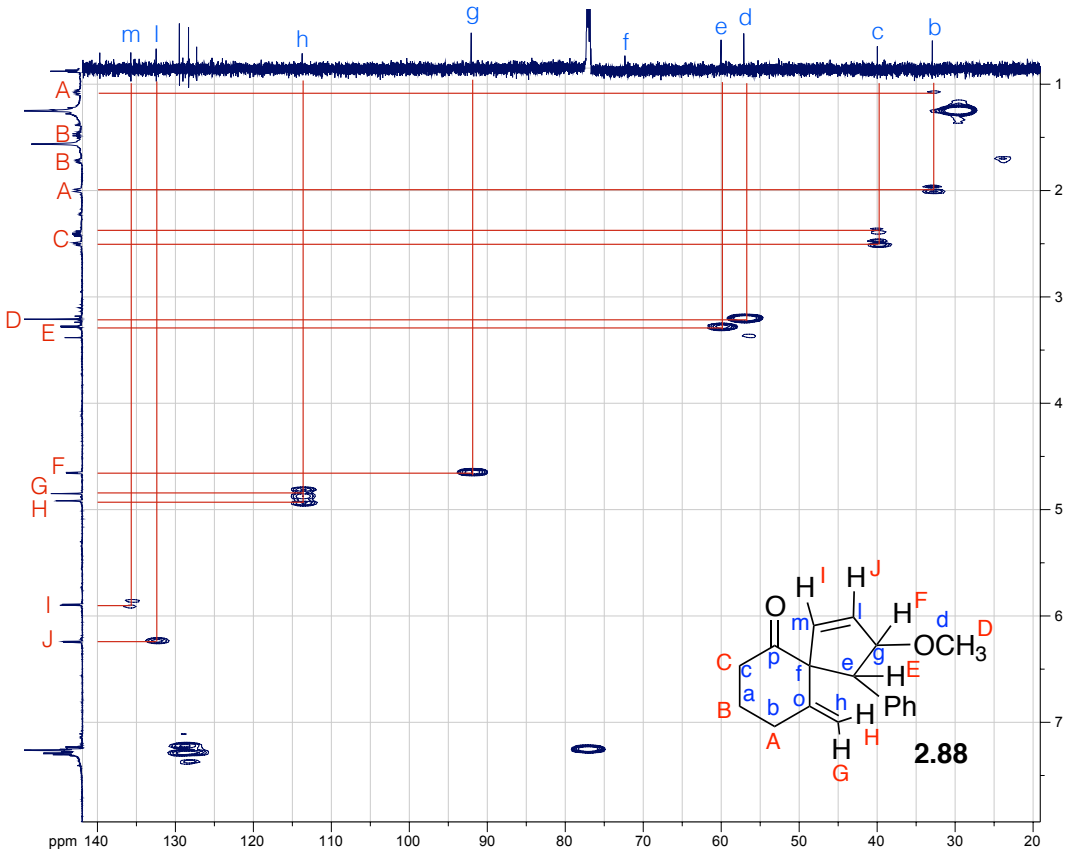


Figure 2.12 HMQC Spectrum of 2.88

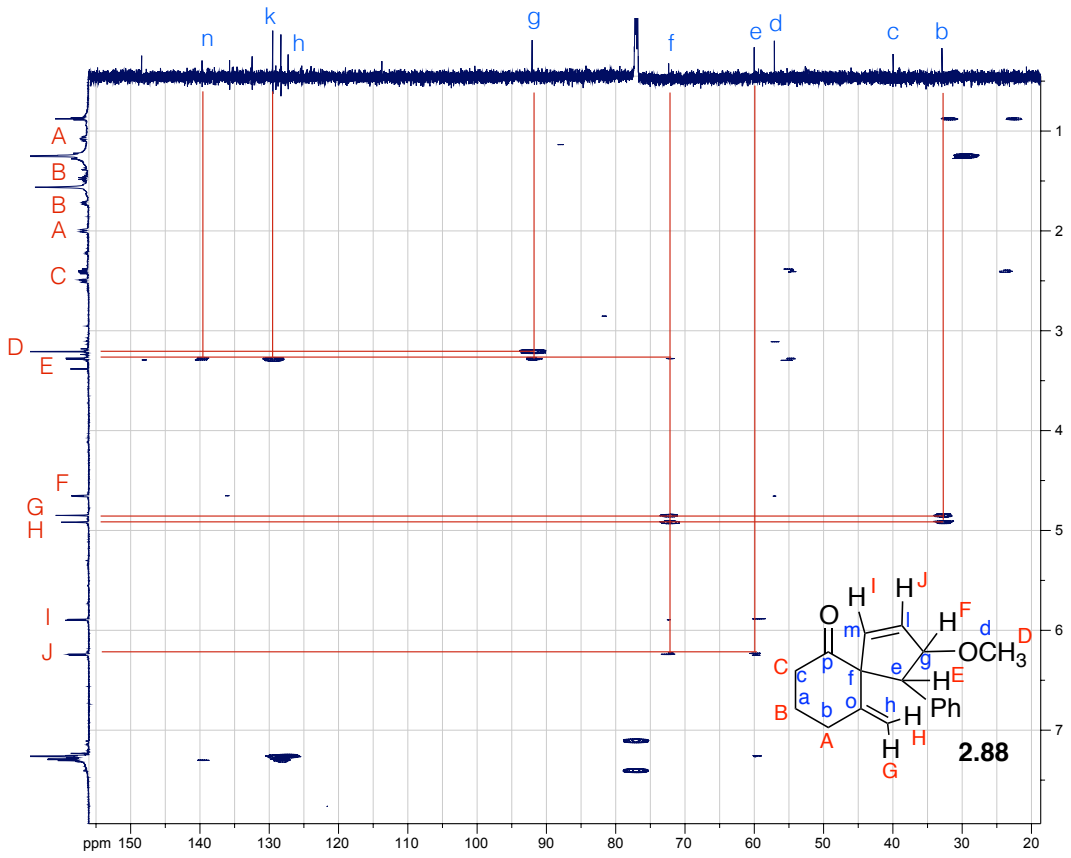
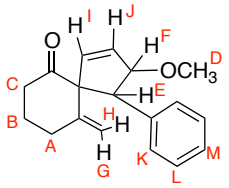
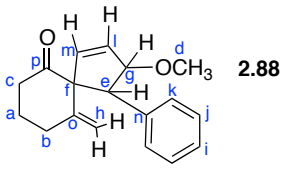


Figure 2.13 HMBC Spectrum of 2.88

Table 2.11 HMBC Correlations for 2.88



Proton Labels



Carbon Labels

2.88

Proton	Observed Coupling With
D	g(^{3}J)
E	f(^{2}J), g(^{2}J), k(^{3}J), n(^{2}J), o(^{3}J)
F	d(^{3}J), m(^{3}J), n(^{3}J)
G, H	b(^{3}J), f(^{3}J)
I	e(^{3}J), f(^{2}J)
J	e(^{3}J), f(^{3}J)

2.5 CONCLUSIONS

The experiments discussed in this chapter provide both computational and experimental data supporting a diradical intermediate in the [2 + 2] cycloaddition reaction of allene-ynes. Tantillo and Siebert performed calculations using B3LYP optimizations on a variety of allene-yne substrates and discovered that in all cases a diradical mechanism is favored; no intermediates from a concerted or zwitterionic mechanism were found. Examining the mechanism experimentally proved to a challenge, however rewarding results were obtained. For the Series A substrates in which a cyclopropane moiety is appended to the allene, the unsubstituted cyclopropane substrate **2.39** and the methoxyphenyl substituted cyclopropane **2.41** produce the [2 + 2] cycloadducts under the reaction conditions. This demonstrates that ring closure to form the four membered ring is extremely fast and occurs at a faster rate than cyclopropane opening. In the case of the diphenyl substituted cyclopropane substrate **2.40**, cyclopropane opening likely occurred as only a trace amount of [2 + 2] cycloadduct was formed. Unfortunately, attempts to separate and characterize the products of the reaction were unsuccessful mainly owing to the "greasy" nature of this substrate. For the Series B substrates, in which a cyclopropane is appended to the alkyne, results of microwave irradiation were quite interesting. In the case of the unsubstituted cyclopropane substrate **2.42**, only the [2 + 2] cycloadduct was formed, which again shows that ring closure to form the four membered ring is faster than opening of the parent cyclopropane. The results of irradiating the diphenyl substituted cyclopropane substrate **2.43** provide evidence for a diradical intermediate. Triene **2.81** was isolated as a mixture of *E* and *Z* isomers; the proposed mechanism for the formation of these products includes the presence of a diradical intermediate, which initiates cyclopropane opening. Finally, the methoxyphenyl cyclopropane substrate **2.44** also provides evidence for a diradical intermediate. The formation of

the fused bicycle **2.87** and spirocycle **2.88** are both rationalized from a mechanism involving a diradical intermediate. No products resulting from an ionic mechanism were found. For the reactions using substrates **2.43** and **2.44** a hydrogen atom transfer species (γ-terpinene) was included in the reaction mixture. In the absence of γ-terpinene a complex mixture of products resulted. Adding the hydrogen atom transfer species did not interfere with cyclopropane opening, but did, however, quench the ring opened products before numerous side-reaction could occur.

3.0 A THERMAL [2 + 2] CYCLOADDITION REACTION FOR THE SYNTHESIS OF SPIRO[BICYCLO[4.2.0]OCTADIENE] INDOLIN-2-ONES AND SPIRO[BICYCLO[5.2.0]NONADIENE] INDOLIN-2-ONES

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Beilstein J. Org. Chem. **2010**, *6*, No. 33

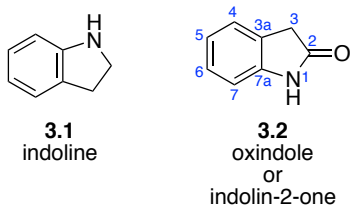
Beilstein J. Org. Chem. **2011**, *7*, 601-605

3.1 BACKGROUND AND INTRODUCTION

The allene-yne [2 + 2] cycloaddition reactions performed in our laboratory provide a quick and convenient method for accessing alkylidene cyclobutenes, with the alkylidene group embedded in a fused six- or seven-membered ring. The progression of this methodology led us to apply it to the synthesis of potentially biologically interesting compounds. The following chapter details our efforts in applying the allene-yne [2 + 2] methodology to the synthesis of spirocyclobutene oxindoles, investigating the chiral transfer from an allene to the bicyclic product in the [2 + 2] cycloaddition reaction, and functionalization of the spirocyclobutene oxindole products.

3.1.1 Nomenclature of Oxindoles and Spirooxindoles

Indolin-2-one (**3.2**), commonly referred to as oxindole, is derived from the parent indoline structure **3.1**, which is a heterocycle consisting of fused benzene and pyrrolidine groups. The oxindole structure **3.2** bears a carbonyl at the 2-position. Numbering of the oxindole compounds is based on the IUPAC recommendation where atom-1 is the nitrogen and atom-2 is the carbonyl carbon with the numbering continuing around the ring. The two carbon atoms at the ring fusion are not given discrete numbers, but each fusion atom is given the same number as the atom immediately preceding it and modified with the letter "a" as shown in Figure 3.1.

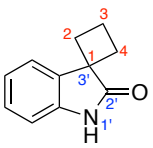


3.1
indoline

3.2
oxindole
or
indolin-2-one

Figure 3.1 Structures of Indoline and Oxindole

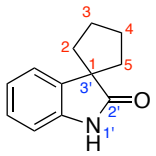
The most common position for substitution on an oxindole is at carbon-3. This is in part due to the relatively high acidity (pK_a = 18) of the protons alpha to the amide and aryl groups. The majority of this chapter will focus on the development of methodology for accessing spirocyclobutene oxindoles, where the spirocycle is attached at C-3 of the oxindole. In the case of these spirocyclic systems, the oxindole numbering is changed to "prime" numbering while the carbocycle gets standard numbering with carbon-1 being designated as the spirocyclic center. The carbon atom at the spirocyclic center is actually numbered twice, once for the carbocycle (C1) and once for the oxindole (C3') as shown in Figure 3.2. Structures such as **3.3** and **3.4** are often referred to by their common names spirocyclobutane oxindole and spirocyclopentane oxindole, respectively (Figure 3.2).



3.3
spiro[cyclobutane-1,3'-indolin]-2'-one
or
spirocyclobutane oxindole

-IUPAC-

-Common-



3.4
spiro[cyclopentane-1,3'-indolin]-2'-one
or
spirocyclopentane oxindole

Figure 3.2 Naming and Numbering Spirooxindoles

3.1.2 Biological Relevance of Oxindoles and Spirooxindoles

Oxindoles are an important class of heterocyclic compounds contained in the core structure of many natural products, as well as pharmaceutically active compounds. There are a number of oxindole containing compounds that are currently used in the treatment of medical conditions. Ropinirole (**3.5**), manufactured by GlaxoSmithKline, is used in the treatment of Parkinson's disease, as well as restless leg syndrome. Ropinirole acts as an agonist at the D2, D3, and D4 dopamine receptors.[49] Before the patent on Ropinirole expired in 2008, it was listed as one of the top 100 drugs based on sales in the United States. Compounds **3.6**, **3.7**, and **3.8** all represent a class of oxindole-containing compounds known as spirooxindoles. Spirooxindole **3.6**, a synthetic compound containing a cyclopropyl ester is known to inhibit the replication of HIV, and possess potent anti-viral activity against other types of viruses.[50] Oxindoles are also present in the core of many natural products including welwitindolinone A isonitrile (**3.7**) and hapalindolinone B (**3.8**). Welwitindolinone A, isolated from blue-green algae,[51] is found to have anti-fungal properties and the ability to reverse P-glycoprotein mediated multiple drug resistance.[52] The hapalindolinone compounds are found to be useful in the treatment of diseases

involving vasopressin including: congestive heart failure, hypertension, and edema (Figure 3.3).[53]

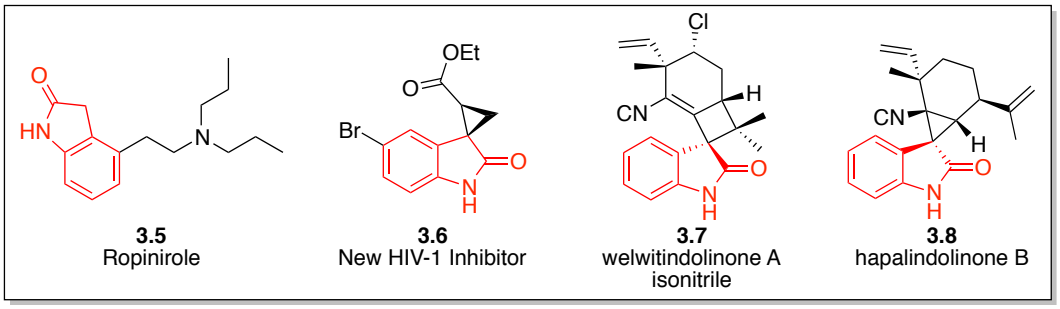


Figure 3.3 Biologically Active Oxindole Containing Pharmaceuticals and Natural Products

Our interest in spirooxindole structures prompted us to search SciFinder for the availability of various heterocyclic and carbocyclic spirooxindole compounds. The search, which is summarized in Figure 3.4, revealed over 40,000 unique compounds.

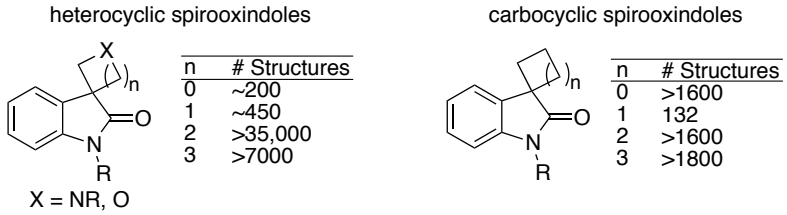


Figure 3.4 Representation of the Number of Spirooxindole Compounds Reported in Literature

The literature concerning the heterospirooxindoles is quite vast, especially for pyrrolidinyl spirooxindole compounds which contains over 35,000 compounds. A discussion of these heterocyclic spirooxindoles is beyond the scope of the current project, but there are available reviews concerning the bioactivity of these compounds.[54] When considering the carbospirocycles, the cyclopropane, cyclopentane, and cyclohexane carbocycles are all well represented in the literature with numbers surpassing one thousand for each class. However, in the case of the spirocyclobutane, just over 100 known compounds and only 43 citations are reported. The lack of representation of the spirocyclobutane oxindole class of compounds

designates it a particularly intriguing synthetic target not only for expansion of synthetic methodology, but also as a pathway to accessing potentially biologically useful compounds that have gone unexplored.

The smallest of the carbocyclic spirooxindole substrates are the compounds containing a spirocyclopropane. A survey of the literature reveals over 1600 compounds possessing this substructure. These compounds hold rich biological activity including: antitumor activity, antidiabetic activity, anti-obesity activity, and an effect on cardiovascular regulation. Spirocyclopropane **3.9** is a potential drug target due to its inotropic properties, which would make the compound valuable in the treatment of congestive heart failure; it is the most potent noncatecholamine, nonglycoside inotrope that they have examined to date.[55] Similar to **3.9**, oxindole **3.10** is substituted at the 5-position of the oxindole. This spirocyclopropane is found to have herbicidal properties, acting via photobleaching and dehydration of plant tissue.[56] Other spirocyclopropane oxindoles, such as **3.11**, have substitution on the cyclopropane ring. This compound was described in a 2007 patent as a potential anti-cancer compound. It was found to inhibit the tyrosine kinase signal transduction pathway, which is involved in the regulation of abnormal cell proliferation.[57] Spirocyclopropane oxindoles are also present in the natural products hapalindolinone A and B (**3.12** and **3.8**), which were extracted from cultured *Hapalosiphon laingii*. These natural products are implicated as vasopressin agonists due to their ability to inhibit binding of vasopressin protein hormone (Figure 3.5).[58]

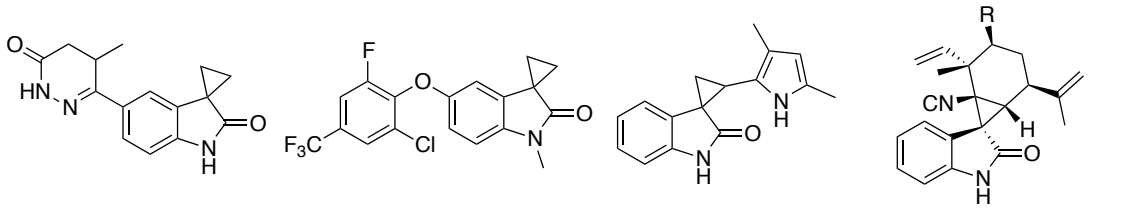


Figure 3.5 Representative Spirocyclopropane Oxindoles

The spirocyclobutane oxindoles are the most rare of the spirooxindole substructures found in chemical literature. Many of the reported spirocyclobutane oxindoles have interesting biological properties and are of current research interest. Interestingly, with the exception of welwitindolinone A (**3.7**), no biological studies have been performed on spirocyclobutane oxindoles with substitution on the cyclobutane ring. This is likely due to the difficulty in accessing these substituted compounds. Figure 3.6 displays some of the more fascinating compounds under investigation. Spirocyclobutane **3.13** is a potent p38α inhibitor. The protein kinase p38α regulates tumor necrosis factor alpha (TNF-α), which is found in excess in inflammatory diseases.[59] Biswasalexin A1 (**3.14**) is an interesting natural product from the phytoalexin family which is found in plants such as wasabi, watercress, and salt cress.[60] Compound **3.15**, containing an aromatic substituent at C-6, was identified for its progesterone receptor agonist activity, working by competitive binding to the progesterone receptor. In this study, it was found that small alkyl or spirocyclic groups at C-3 of the oxindole had the highest activity.[59] The spirocyclobutane oxindole **3.16** with a pyridazone at C-6 was found to contain inotropic properties, and is a potential drug target for chronic management of congestive heart failure.[55] In 2007, Lilly Research Laboratories reported spirooxindole compounds such as **3.17**, which were demonstrated to have β_3 agonist activity. Stimulation of β_3 adrenergic receptor results in an increase of fatty acid oxidation and an increase in energy expenditure. These

compounds may have therapeutic value as weight loss supplements.[61] Spirocyclobutane oxindole compounds containing a thiazole at C-6, as in **3.18**, were found to have anti-inflammatory activity by inhibition of gamma interferon (INF-ϒ), as well as TNF-α (Figure 3.6).[62]

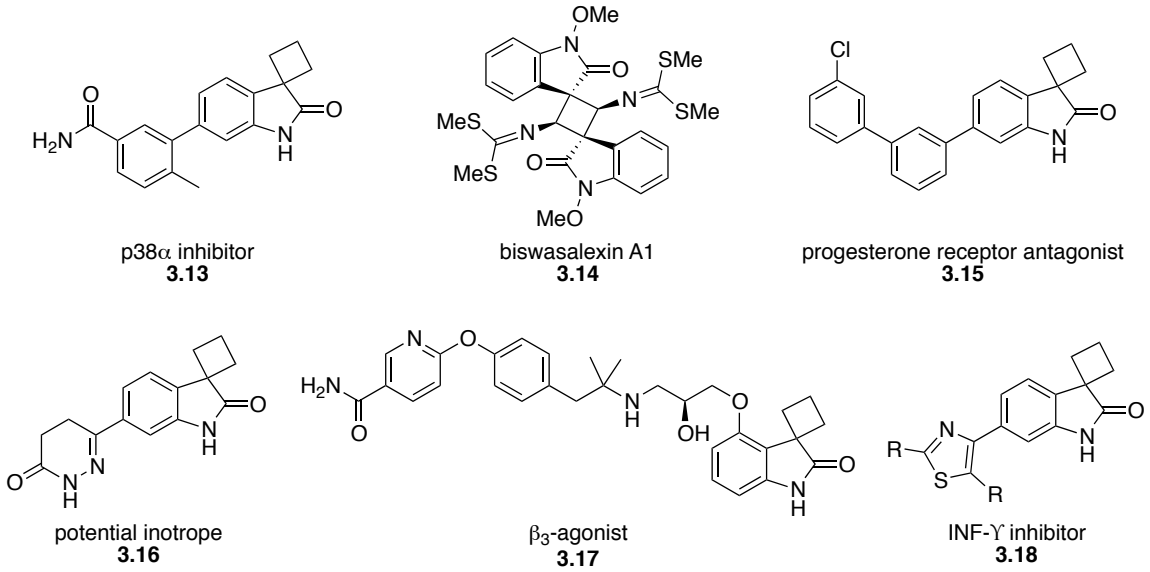


Figure 3.6 Representative Spirocyclobutane Oxindoles

The most prevalent class of carbocyclic spirooxindoles is the spirocyclopentane oxindole compounds. A SciFinder search reveals over 1600 compounds containing the spirocyclopentane oxindole core, with nearly 600 references pertaining to the bioactivity of these compounds. Figure 3.7 shows two biologically active spirocyclopentane oxindoles. Compound **3.19**, described in a 2008 patent, is valuable in treating diseases where the calcitonin gene-related peptide (CGRP) is involved, such as in headaches and migraines.[63] Spirocyclopentane oxindoles of the structure **3.20** contain a carboxylate substituent on the cyclopentane ring. These compounds were discovered to be useful in the treatment of hypertension (Figure 3.7).[64]

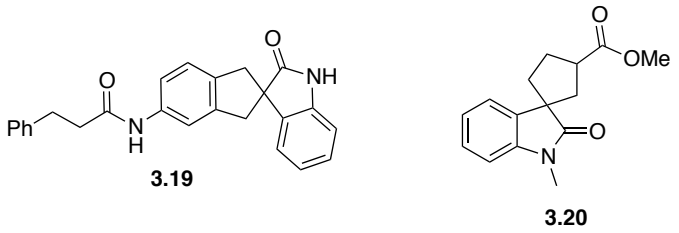


Figure 3.7 Representative Spirocyclopentane Oxindoles

While most biologically active spirooxindole compounds possess a free NH on the oxindole, there are a handful of biologically useful compounds that contain substitution at the nitrogen atom. Gelsemoxonine (**3.21**), a natural product isolated from the leaves of *Gelsemium elegans,* is a bicyclospirooxindole with a methoxy group attached at the oxindole nitrogen. This compound is employed in traditional Chinese medicine, and is currently being studied as a new antitumor lead compound.[65] Compound **3.22**, containing a hydroxymethyl group appended to the oxindole nitrogen, was the subject of a recent patent and was established as an MDM2-p53 inhibitor, which makes it potentially advantageous in the treatment of cancer.[66] Spirocyclobutane oxindole **3.23**, containing a sulfone substituent on the amide nitrogen is reported to be agonistic at the oxytocin receptor, making it potentially effective in the treatment of dementia and related diseases (Figure 3.8).[67]

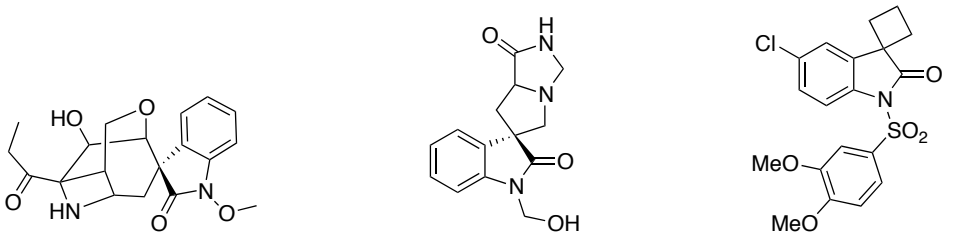


Figure 3.8 Spirooxindoles Containing Substitution at the Oxindole Nitrogen

3.1.3 Synthetic Access to Spirocyclobutane Oxindoles

The spirocyclobutane oxindoles intrigued us from both a biological and synthetic standpoint. As discussed above, these compounds have interesting biological properties including: antifungal activity, anti-inflammatory activity, and inotropic activity. From a synthetic perspective, we are interested in cyclobutene and cyclobutane containing compounds because our allene-yne [2 + 2] cycloaddition reaction affords rapid entry into often molecularly complex cyclobutene containing products. Moreover, the two double bonds of the alkylidene cyclobutene have the potential to undergo transformation to functionalized cyclobutane containing substrates (Figure 3.9).

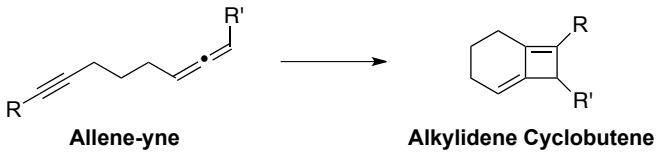


Figure 3.9 Allene-yne [2 + 2] Cycloaddition Reaction

A common method for accessing spirocyclobutane oxindoles is through the dimerization reaction of 3-methylene substituted oxindoles. In 1994, Pilati generated a 3-allenyl oxindole *in situ* from chloroalkene **3.24**. Under the reaction conditions, an intermolecular allene-allene [2 + 2] cycloaddition reaction occurred to provide **3.25**, as well as the other, head-to-tail [2 + 2] cycloadduct (Figure 3.10 A).[68] In a later example, Milanesio demonstrated the formation of a spirocyclobutane oxindole dimer **3.27** by subjecting **3.26** to photochemical initiation, which prompted an intermolecular alkene-alkene [2 + 2] cycloaddition reaction (Figure 3.10 B).[69]

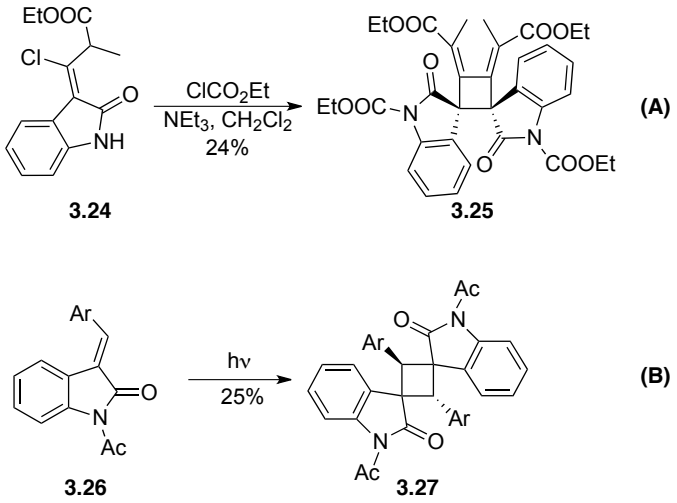


Figure 3.10 Synthesis of Spirocyclobutane Oxindoles via Dimerization Reactions

The two most common methods for forming non-dimeric spirocyclobutane oxindoles are shown in Figure 3.11. Storey demonstrated in 1995 that under radical initiation conditions, the aryl radical of **3.28** is formed; the radical subsequently cyclizes to form spirocycle **3.29** (Figure 3.11 A).[70] Alkylation chemistry has also been used to form spirocyclobutane oxindoles. Reacting oxindole **3.30** with two equivalents of 1,3-diiodopropane resulted in the formation of spirocycle **3.31** in low yield (Figure 3.11 B).[71]

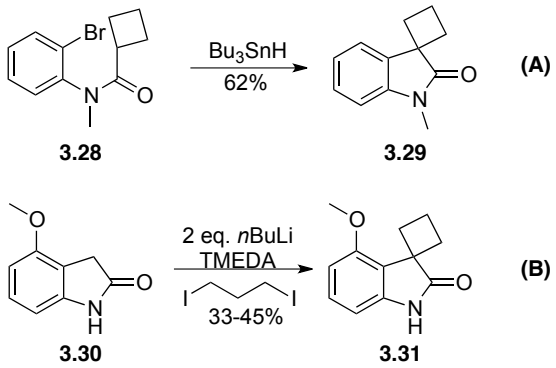


Figure 3.11 Synthesis of Spirocyclobutane Oxindoles under Radical and Alkylation Conditions

One of the earliest examples for forming a spirocyclobutane oxindole was reported by Righetti in 1981. This method involved nucleophilic addition of ethyl vinyl ether into the alkene

of **3.32**, providing a dicyano stabilized carbanion and oxocarbenium ion. Addition of the carbanion into the oxocarbenium ion provided spirocycle **3.33** (Figure 3.12).[72]

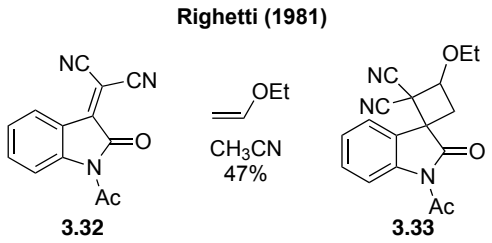
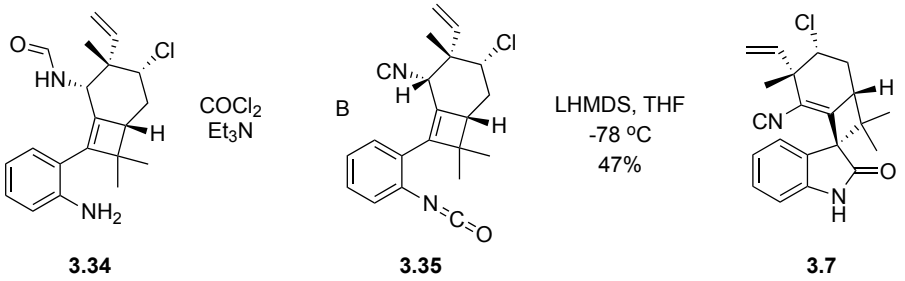


Figure 3.12 Formation of a Spirocyclobutane Oxindoles via a Zwitterionic Intermediate

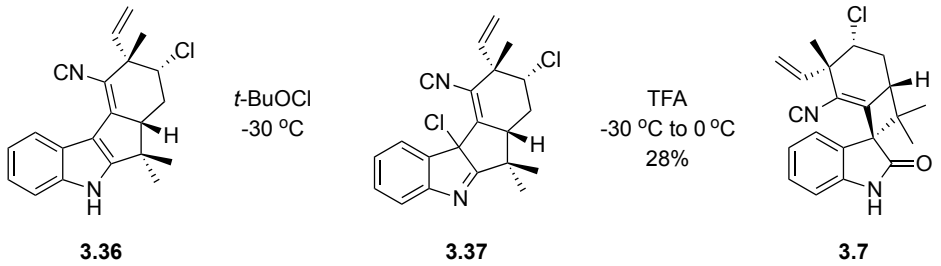
More specialized methods for forming spirocyclobutane oxindoles have also been described. These examples include Wood and Baran's syntheses of welwitindolinone A isonitrile (**3.7**), which required the formation of the spirocyclobutane core in this interesting natural product. Wood's synthesis commenced with highly functionalized compound **3.34**, which was converted to **3.35** by reaction with phosgene/triethylamine, affecting formation of both the isonitrile and isocyanate. The intermediate isocyanate **3.35** was immediately exposed to basic conditions, furnishing the spirocyclobutane oxindole **3.7**, welwitindolinone A isonitrile, as a single diastereomer (Scheme 3.1).[73]



Scheme 3.1 Wood's Synthesis of the Spirocyclobutane in Welwitindolinone A

In Baran's undertaking of the synthesis of welwitindolinone A, indole **3.36** was converted to a presumed intermediate **3.37** through a chlorination reaction using *t*-butyl hypochlorite. Intermediate **3.37** is proposed to undergo a skeletal reorganization affording spirocyclobutane

oxindole **3.7**. This transformation provided a 10:1 ratio of spirooxindole diastereomers, with welwitindolinone A isonitrile (**3.7**) being the major isomer (Scheme 3.2).[74]



Scheme 3.2 Baran's Synthesis of the Spirocyclobutane in Welwitindolinone A

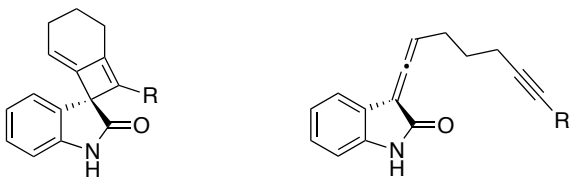
While there are a variety of methods to produce spirocyclobutane oxindoles, the generality of these methods is quite limited. In many cases, only unfunctionalized spirocyclobutanes can be produced, which results in products with limited synthetic utility. More highly functionalized products can be obtained, but highly specific procedures had to be developed for application to the natural product welwitindolinone A. Although the dimerization reactions provide functionalized cyclobutane products, dimeric compounds often have limited synthetic value as they are often difficult to further functionalize and are generally not applicable to pharmaceuticals.

3.2 A TANDEM [3,3]-SIGMATROPIC REARRANGEMENT/[2 + 2] CYCLOADDITION TO ACCESS SPIROCYCLOBUTENE OXINDOLES

3.2.1 Application of the Allene-yne [2 + 2] Methodology in the Synthesis of Spirocyclobutene Oxindoles

Current methods for the preparation of carbocyclic spirooxindoles are quite limited and provide either relatively unfunctionalized products or require highly specialized reaction protocols. The chemical space containing spirocyclobutane oxindoles is quite sparse, with just over 100 known compounds, despite their often-rich biological activity. To further expand the available pool of spirocyclobutane oxindoles for chemical as well as biological evaluation studies, a novel method for their preparation must be developed. An ideal method will provide structurally complex, highly functionalized, unsymmetric spirocyclobutane oxindole compounds in relatively few steps from simple starting materials.

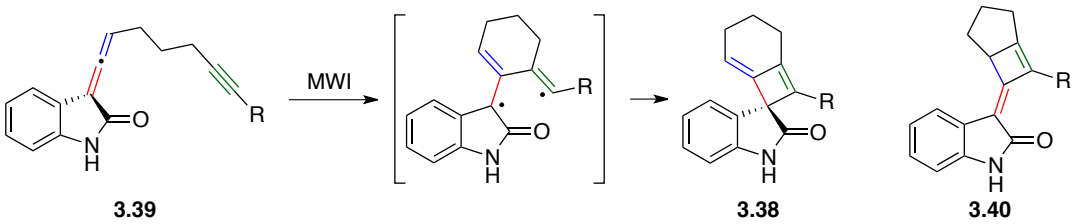
Utilizing the thermal allene-yne [2 + 2] cycloaddition reaction developed in our group, we envisioned that the preparation of a spirocyclobutene oxindole **3.38** could be achieved from 3-allenyl substituted oxindole **3.39** via a thermal [2 + 2] cycloaddition reaction as shown in Scheme 3.3.



3.38 **3.39**

Scheme 3.3 Proposed Synthesis of Spirocyclobutane Oxindoles via an Allene-yne [2 + 2] Cycloaddition Reaction

Based on our previous studies of the intramolecular allene-yne [2 + 2] cycloaddition, reaction of the alkyne should occur with the distal double bond (red) of the allene to provide spirooxindole **3.38**. Reaction of the alkyne with the proximal double bond (blue) would provide **3.40**, but this reaction should not occur under the aforementioned conditions. It should be pointed out that examples possessing 1,1,3-trisubstituted allenes, such as **3.39**, have not been previously investigated. However, if the reaction proceeds via a biradical as evidence has suggested, the corresponding biradical intermediate should be even more stable than that in the disubstituted allene (Scheme 3.4).



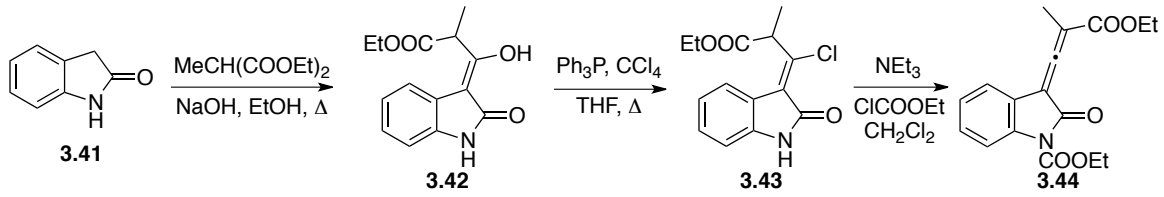
Scheme 3.4 [2 + 2] Cycloaddition with the Proximal versus Distal Allene Double Bond

The [2 + 2] cycloaddition reaction to form spirocyclobutene oxindoles such as **3.38** is attractive for a myriad of reasons. First, these compounds have two endocyclic double bonds, which makes them potentially useful in the formation of highly functionalized ring systems. For example, it is envisioned that the double bonds will participate in: epoxidation, dihydroxylation, aziridination, cyclopropanation, and hydroboration reactions. Additionally, little is known about the synthetic utility and reactivity of alkylidene cyclobutenes. Preparing spirooxindoles such as **3.38** will allow for exploration of the scope and limitations of this moiety. Next, it was anticipated that if a chiral allene **3.39** were prepared, transfer of chiral information from the allene to the spirooxindole **3.38** might be possible providing an enantioenriched spirocyclobutene oxindole. To date, there are no general methods for accessing spirocyclobutane oxindoles in an enantioselective manner. Finally, we were intrigued by the similarity of spirocyclobutene **3.38** to

the core of the natural product welwitindolinone A isonitrile (**3.7**). If transfer of chirality from allene-yne **3.39** to spirocyclobutane **3.38** is successful, and functionalization of the double bonds proves versatile, synthesis of natural product **3.7** would become a feasible goal.

3.2.2 Efforts to Prepare a 3-Allenyl Substituted Oxindole

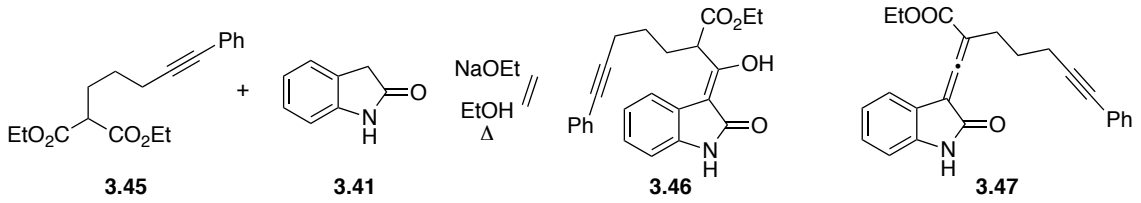
Oxindoles with an allene fused to the 3-position are extremely rare. To date, only a single example for preparing this type of structure has been reported in the literature.[68] In 1994, Beccalli and coworkers reported a vinyl chloride elimination protocol to produce allene **3.44**. Starting from oxindole (**3.41**), enol **3.42** was prepared by refluxing in the presence of sodium ethoxide and diethyl 2-methylmalonate. The alcohol of **3.42** was then converted to a chloride yielding **3.43** via an Appel reaction. Finally, treating vinyl chloride **3.43** to basic conditions resulted in the formation of allenyloxindole **3.44** in 13% yield (Scheme 3.5).



3.41 **3.42** **3.43** **3.44**

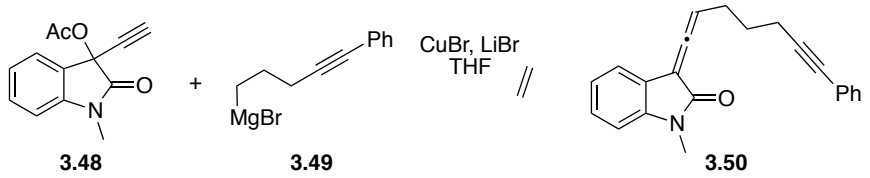
Scheme 3.5 Beccalli's Synthesis of a 3-Allenyl Oxindole

Our initial strategy for accessing 3-allenyloxindole **3.47** was based on Beccalli's work. It was reasoned that refluxing malonate **3.45** and oxindole **3.41** in a solution of sodium ethoxide and ethanol would provide substrate **3.46**, which could then be further transformed into allene **3.47**. Unfortunately, all attempts at synthesizing enol **3.46** were unsuccessful, leading to recovery of starting material. The same reaction was performed employing Boc-protected oxindole, but a complex mixture of products resulted (Scheme 3.6).



Scheme 3.6 Attempted Preparation of Allenyl Oxindole 3.47

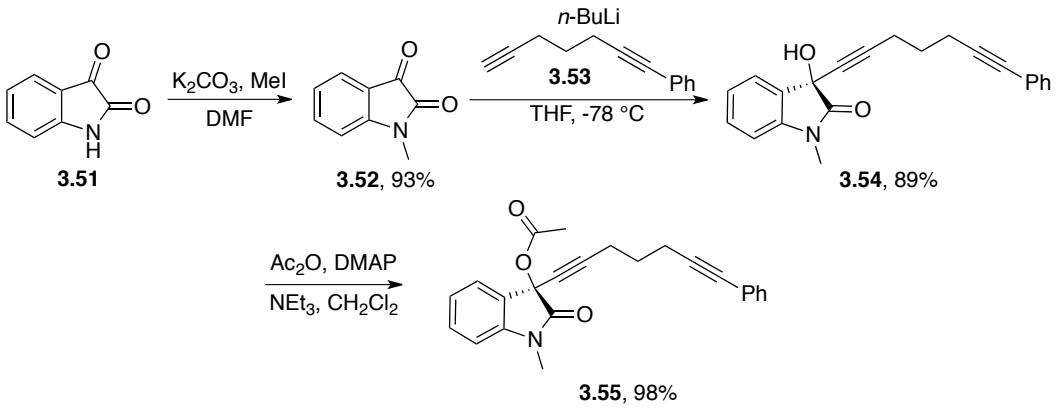
The next pathway to accessing a 3-allenyloxindole was investigated using cuprate chemistry. Treating Grignard reagent **3.49** to CuBr/LiBr conditions should result in the formation of the lower order cuprate. This cuprate was envisioned to add into the propargyl acetate **3.48** forming allene **3.50** via an S_N2' mechanism.[75] Unfortunately, no desired product **3.50** was observed under these conditions. Analysis of the reaction mixture by TLC and ^{1}H NMR spectroscopy revealed recovered starting material **3.48** and no desired allene product (Scheme 3.7).



Scheme 3.7 Attempted Preparation of Allenyl Oxindole 3.50

We next turned our attention to metal-catalyzed rearrangement reactions of propargyl acetates to allenyl acetates with hopes of accessing a 3-allenyloxindole. The propargyl acetate substrate **3.55** used in this investigation was prepared as depicted in Scheme 3.8, and began by the methylation of isatin **3.51** with iodomethane and potassium carbonate in DMF. The methylation proceeded to provide **3.52** in an excellent 93% yield.[76] Next, the lithiate of diyne **3.53** was added to *N*-methylisatin (**3.52**), providing propargyl alcohol **3.54** in 89% yield. The formation of **3.54** was confirmed by a new alcohol proton resonance in the ^{1}H NMR spectrum at δ 3.48 and new alkyne carbon resonances in the ^{13}C NMR spectrum at δ 88.9, 86.5, 81.1, and

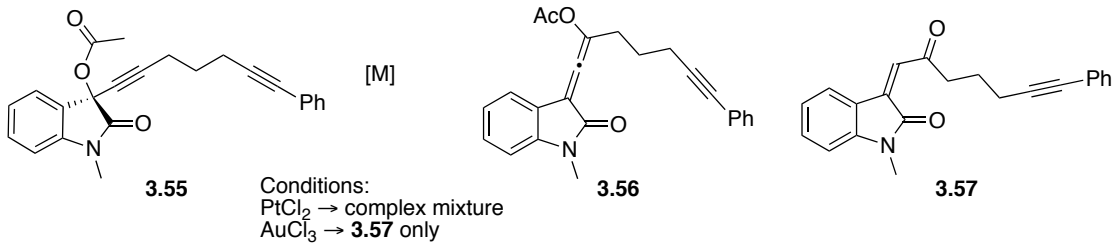
69.0. Finally, reacting propargyl alcohol **3.54** with acetic anhydride, triethylamine, and catalytic DMAP in dichloromethane provided the desired propargyl acetate **3.55** in 98% yield. Formation of **3.55** was confirmed based on the disappearance of the alcohol proton resonance and appearance of a new acetate methyl resonance at 2.09 ppm in the ^{1}H NMR spectrum (Scheme 3.8).



Scheme 3.8 Preparation of Propargyl Acetate 3.55

With propargyl acetate **3.55** in hand, we turned our attention to a metal-catalyzed rearrangement reaction.[77] First, platinum(II) chloride was utilized in the reaction. Under thermal conditions, the reaction progressed slowly. After one day of heating, starting material **3.55** had been completely consumed, but a complex mixture of products was observed. Based on the ^{1}H NMR spectra of the isolated products, both allenyl acetate **3.56** and the hydrolysis product **3.57** were generated during the reaction. Unfortunately, isolation of pure allenyl acetate **3.56** by column chromatography was not successful. Next, reaction with gold(III) chloride was investigated. The reaction of propargyl acetate **3.55** with $AuCl_3$ in toluene at room temperature resulted in the formation of only the hydrolysis product **3.57** in 65% yield as a single isomer based on the crude ^{1}H NMR spectrum. The vinyl proton resonance in **3.57** appeared as a distinct

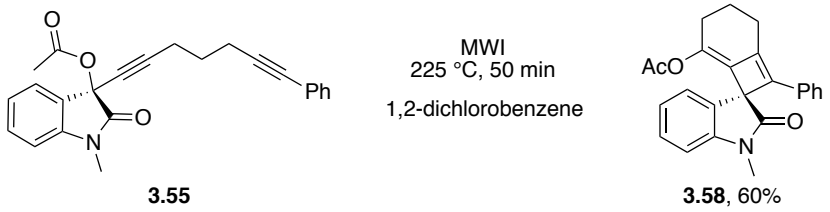
singlet at δ 7.23 in the ^{1}H NMR spectrum. No allenyl acetate **3.56** was detected in the reaction mixture, and performing the reaction at 0 °C resulted in no reaction (Scheme 3.9).



Scheme 3.9 Results of Subjecting Propargyl Acetate 3.55 to Transition Metal Conditions

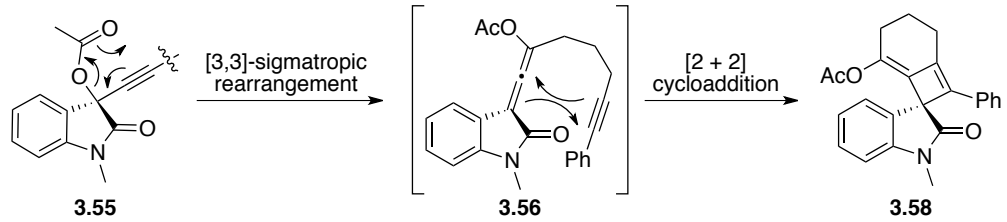
3.2.3 Investigating The Thermal [3,3]-Sigmatropic Rearrangement of Propargyl Acetates to Allenyl Acetates

The difficulty we found preparing an allenyl oxindole via a metal catalyzed process prompted us to reexamine the literature for alternative, less traditional methods for accessing this moiety. One of the more intriguing discoveries was scattered reports of thermal [3,3]-sigmatropic rearrangements of propargyl acetates to form allenyl acetates.[78] Although there was limited precedence for this thermal transformation, we chose to investigate it utilizing propargyl acetate **3.55**. Microwave irradiation of **3.55** for 50 min at 225 °C resulted in the formation of spirooxindole **3.58** in 60% yield (Scheme 3.10).



Scheme 3.10 Formation of Spirocyclobutene Oxindole 3.58 Under Microwave Conditions

We propose that the spirooxindole **3.58** is formed via the mechanism shown in Scheme 3.11. Upon heating, propargyl acetate **3.55** undergoes a [3,3]-sigmatropic rearrangement. The intermediate allenyl acetate **3.56** is immediately consumed in an intramolecular [2 + 2] cycloaddition reaction with the tethered alkyne to provide spirocyclobutene oxindole **3.58**. Analysis of the reaction mixture revealed that all starting material had been consumed, and no allenyloxindole **3.59** was detected, presumably because the [2 + 2] cycloaddition step occurs at a faster rate than the [3,3]-sigmatropic rearrangement (Scheme 3.11).

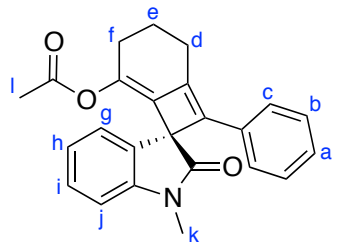


3.55 **3.56** **3.58**

Scheme 3.11 Proposed Mechanism for the Formation of Spirooxindole 3.58

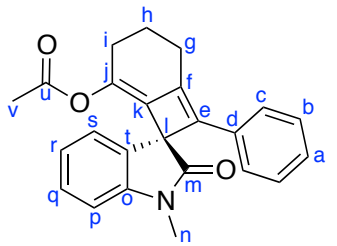
Structural confirmation of spirocyclobutene oxindole **3.58** was achieved using ^{1}H and ^{13}C NMR spectroscopy, as well as 2D NMR spectroscopy including: COSY, HMQC, and HMBC. Additionally, high-resolution mass and IR data were obtained. Tables 3.1 and 3.2 include the ^{1}H and ^{13}C NMR structural assignments for this compound.

Table 3.1 ^{1}H NMR Assignments for Spirocyclobutane Oxindole 3.58



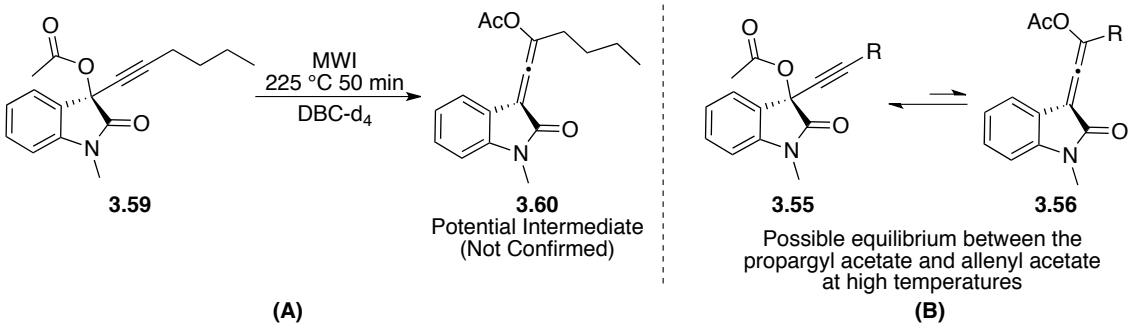
Proton	Chemical Shift (ppm)	Multiplicity	Integration	*J*-Value (Hz)
a	7.08	t	1H	7
b	7.15	t	2H	7.7
c	6.87	d	2H	8.4
d	2.79 – 2.67	m	2H	-
e	2.17 – 2.03	m	2H	-
f	2.42 – 2.34	m	2H	-
g	7.17	d	1H	7.7
h	6.98	t	1H	7.7
i	7.29	t	1H	7.7
j	6.90	d	1H	8.4
k	3.34	s	3H	-
l	1.77	s	3H	-

Table 3.2 ^{13}C NMR Assignments for Spirocyclobutane Oxindole 3.58



Carbon	Chemical Shift (ppm)	Carbon	Chemical Shift (ppm)
a	127.1	l	61.8
b	128.5	m	175.5
c	125.4	n	26.7
d	132.7	o	143.8
e	137.7	p	107.8
f	147.0	q	128.5
g	22.3	r	122.4
h	23.7	s	123.5
i	27.3	t	127.6
j	132.0	u	167.3
k	124.5	v	20.5

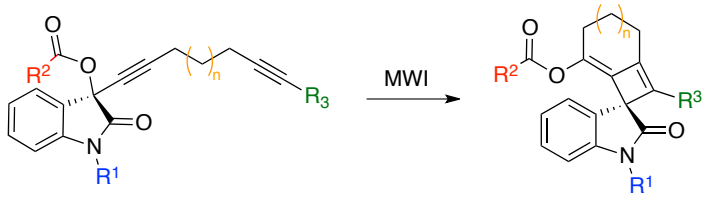
To further investigate the presence of the proposed allenyl acetate intermediate, we attempted direct formation of the allene under the thermal conditions employing propargyl acetate **3.59**, which does not contain the tethered alkyne and therefore cannot undergo a [2 + 2] cycloaddition reaction. Based on the proposed mechanism in Scheme 3.11, propargyl acetate **3.59** should undergo a thermal [3,3]-sigmatropic rearrangement to produce allenyl acetate **3.60**. This reaction was performed while being monitored by ^{1}H NMR analysis. Although there are signals that could correspond to allenyl acetate **3.60**, analysis of the reaction mixture showed that substantial decomposition had occurred (Scheme 3.12 A). Features in the crude ^{1}H NMR spectrum indicating the formation of the allenyl acetate include a downfield shift of the acetate resonance from δ 1.81 to δ 2.40. Also, there was a downfield shift observed in the resonances for the propargyl protons on conversion to the allene from δ 2.02 to δ 2.72. There was also a second unidentified compound observed in the crude ^{1}H NMR spectrum with a resonance portraying an acetate CH_3 group. Efforts to isolate these compounds by silica gel chromatography were unsuccessful. The inability to access the allenyl acetate under metal-catalyzed or thermal conditions (see Scheme 3.9), led us to conclude that oxindoles substituted with an allenyl acetate at the 3-position are quite reactive. In the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction, the allenyl acetate was formed then immediately consumed via a [2 + 2] cycloaddition reaction with the tethered alkyne. Alternatively, an equilibrium between the propargyl acetate **3.55** and allenyl acetate **3.56** may exist at high temperatures. If the equilibrium favors the propargyl acetate **3.55**, this would explain why the allenyl acetate **3.56** is never observed in the reaction to form spirooxindoles (Scheme 3.12 B).



Scheme 3.12 Thermal [3,3]-Sigmatropic Rearrangement of 3.59

3.2.4 Exploring the Scope and Limitations of the Tandem [3,3]-Sigmatropic Rearrangement/[2 + 2] Cycloaddition Reaction to Form Spirocyclobutene Oxindoles

One incentive for the further development of the [2 + 2] cycloaddition reaction in the formation of spirocyclobutene oxindoles is the potential application of our methodology to the synthesis of a library of unique substrates possessing biologically interesting properties. The first generation diversifications of the spirooxindole scaffold are shown in Figure 3.13. These include varying the amide nitrogen substituent (R^1), the ester (R^2), the cyclobutene substituent (R^3) and the size of the fused ring (n). These variations were chosen to expand the scope of the [2 + 2] cycloaddition reaction with an eye towards the synthesis of biologically relevant compounds (Scheme 3.13).



Scheme 3.13 Sites of Diversification in the Spirooxindole

3.2.4.1 Preparation of the Spirooxindole Precursors With Group Variations at the Oxindole Nitrogen (R^1)

Protection of the oxindole nitrogen was a requirement during the preparation of the spirooxindole precursors, as the N-H was not compatible with the reaction conditions to form the propargyl acetate. However, we were interested in having a protecting group that could be removed under mild conditions to provide the unprotected oxindole. To achieve the most versatility, we prepared substrates with methyl, methoxymethyl (MOM), 2-(trimethylsilyl)ethoxymethyl (SEM), and acetate (Ac) groups as the R^1 substituents.

Propargyl acetates **3.67**, **3.68**, and **3.69** with substituent variations at the oxindole amide (R^1) were all prepared in an analogous manner (Scheme 3.14). Preparation of propargyl acetate **3.67** initiated with a methoxymethyl (MOM) protection of isatin (**3.51**) employing sodium hydride and methoxymethyl chloride (MOM-Cl) in THF which provided MOM-isatin **3.61** in a 75% yield.[79] Next, diyne **3.53** was reacted with *n*-butyllithium in THF at -78 °C to form the lithiated diyne. Subsequent addition of *N*-MOM isatin **3.61** as a solution in THF resulted in formation of propargyl alcohol **3.64** in a 75% yield. Formation of **3.64** was confirmed by ^{1}H and ^{13}C NMR spectroscopy and IR. A defining spectroscopic feature of propargyl alcohol **3.64** was the diastereotopicity of the methylene protons on the MOM moiety. The diastereotopic resonances were observed as doublets at δ 5.16 and 5.11 in the ^{1}H NMR spectrum. This diastereotopic splitting pattern was a characteristic of every MOM-containing propargyl substrate that we prepared. Additionally, triplets at δ 2.48 and 2.41 corresponding to the methylene groups adjacent to the alkynes were observed in the ^{1}H NMR spectrum. Analysis of the ^{13}C NMR spectrum showed the disappearance of the isatin C-3 carbonyl at δ 182.8 and the appearance of a quaternary carbon resonance at δ 77.2. The transformation from isatin to an

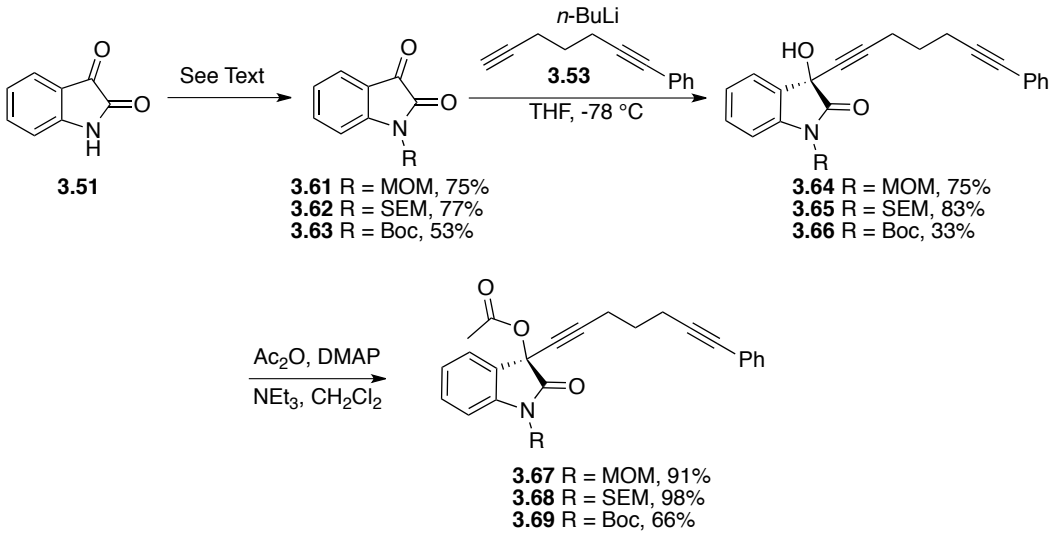
oxindole also resulted in a characteristic downfield shift of the amide carbonyl carbon from δ 158.4 to 174.8. A final piece of data supporting the formation of propargyl alcohol **3.64** was the characteristic –OH stretch in the IR spectrum at 3374 cm^{-1}. The next step in the synthetic sequence was acylation of propargyl alcohol **3.64** utilizing acetic anhydride, triethylamine, and catalytic 4-dimethylaminopyridine (DMAP) in dichloromethane providing propargyl acetate **3.67** in 91% yield (Scheme 3.14). The characteristic NMR resonances supporting the formation of **3.67** included the appearance of the acetate methyl resonance at δ 2.11 in the ^{1}H NMR spectrum and at δ 27.1 in the ^{13}C NMR spectrum. Additionally, the ^{13}C NMR spectrum showed a new resonance at δ 168.5, which corresponded to the carbonyl carbon of the acetate. In the IR spectrum, disappearance of the –OH stretch, and appearance of a new carbonyl stretch at 1746 cm^{-1} were observed.

Propargyl acetate **3.68**, containing a 2-(trimethylsilyl)ethoxymethyl (SEM) protecting group was prepared in a manner similar to that described for **3.67**. First, isatin (**3.51**) was treated with sodium hydride and 2-(trimethylsilyl)ethoxymethyl chloride (SEMCl) in DMF to provide the protected amide **3.62** in 77% yield.[80] Next, the lithium acetylide of **3.53** was formed by reacting diyne **3.53** in THF with *n*-butyllithium at -78 °C. Subsequent addition of SEM-isatin **3.62** provided the propargyl alcohol **3.65** in 83% yield. Formation of **3.65** was supported by ^{1}H NMR analysis. Resonances for the protons on the carbon atoms adjacent to the alkyne moieties appeared as distinct triplets at δ 2.48 and 2.41. The SEM group also displayed characteristic resonances in the ^{1}H NMR spectrum. As with the MOM protected substrates, the SEM substrates containing a chiral center at C-3 possessed diastereotopic resonances, corresponding to the SEM methylene protons, which were observable by ^{1}H NMR spectroscopy; these diastereotopic protons appeared as doublets at δ 5.18 and 5.12. The SEM group also possessed two $–CH_2$

resonances at δ 3.59 and 0.92, and a TMS singlet at δ -0.04 in the ^{1}H NMR spectrum. The final step of the synthetic sequence was acetylation of alcohol **3.65** using acetic anhydride, triethylamine, and catalytic DMAP in dichloromethane to generate propargyl acetate **3.68** in a 98% yield. The key resonance in the ^{1}H NMR spectrum supporting the formation of **3.68** was the appearance of a methyl group belonging to the acetate, which was observed at δ 2.10. Additionally, the IR spectrum of propargyl acetate **3.68** revealed a new carbonyl stretch at 1747 cm^{-1}, as well as the absence of an –OH stretch (Scheme 3.14).

Propargyl acetate **3.69**, containing the *t*-butoxycarbonyl (Boc) protected indole, was prepared beginning with a Boc protection of isatin (**3.51**). Reacting isatin (**3.51**) with di-*t*-butyldicarbonate and DMAP in THF provided Boc-isatin **3.63** in a 53% yield within 3 hours.[81] The lithium acetylide of **3.53** was reacted with Boc-isatin **3.63** providing the propargyl alcohol **3.66** in a low, 33% yield. Nucleophiles, including R-Li, are known to deprotect Boc-amides, likely contributing to the low yield.[82] A resonance appearing as a singlet at δ 10.7 in the crude ^{1}H NMR spectrum corresponding to the –NH of the unprotected oxindole compound supported this hypothesis. The deprotection of the Boc group under the reaction conditions was unfortunate in that pure propargyl alcohol **3.66** could not be obtained even after column chromatography. However, characteristic resonances in the ^{1}H NMR spectrum supported the presence of the desired product. The resonances included triplets at δ 2.72 and 2.62 in the ^{1}H NMR spectrum corresponding to the $–CH_2$ groups adjacent to the two alkynes. Also, the resonances for the *t*-butyl protons of the Boc group appeared as a singlet at δ 1.55 in the ^{1}H NMR spectrum. The impure propargyl alcohol **3.66** was subjected to to the acetylation conditions previously described to afford propargyl acetate **3.69** in 66% yield. Based on the ^{1}H NMR spectrum a *ca*. 4:1 ratio of rotamers existed at room temperature. Compounds containing Boc-protected amides

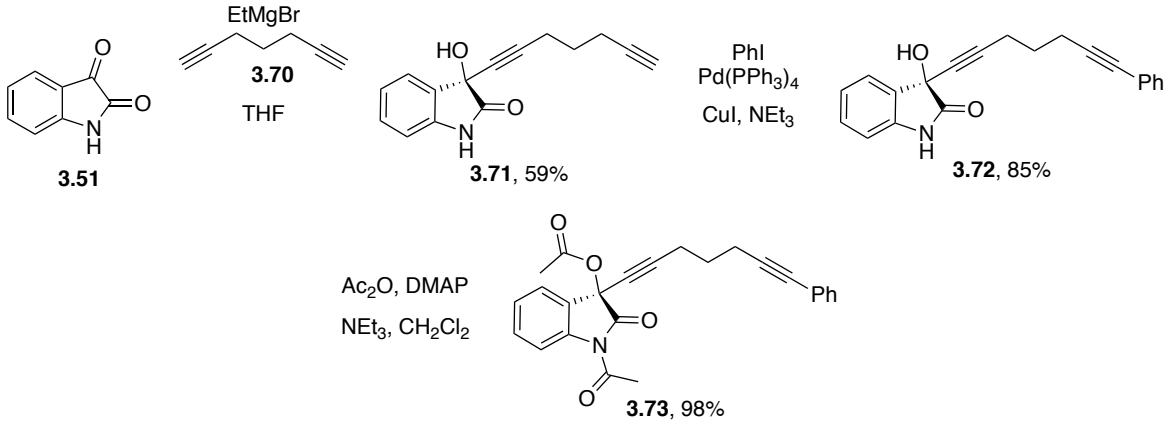
often exist as a mixture of rotamers with broadened resonances due to hindered rotation. The characteristic resonances supporting formation of propargyl acetate **3.69** were the two rotameric acetate methyl singlets at δ 2.14 and 2.12 in the ^{1}H NMR spectrum (Scheme 3.14).



Scheme 3.14 Preparation of Propargyl Acetates 3.67, 3.68, and 3.69

Preparation of propargyl acetate **3.73**, containing the acetyl protected oxindole nitrogen, is shown in Scheme 3.15. Ethyl magnesium bromide was added to a room temperature solution of 1,6-heptadiyne (**3.70**) in THF to form an alkynyl Grignard species. Isatin (**3.51**) was then added as a solution in THF to provide propargyl alcohol **3.71** in 59% yield. The moderate yield of the reaction was attributed to di-addition of the **3.70**, forming a symmetrical byproduct containing the oxindole substituent at both alkyne termini. Formation of alcohol **3.71** was confirmed by ^{1}H NMR spectroscopy, with new resonances appearing at δ 2.30 (t) and 2.19 (dt) corresponding to the –CH_2 groups adjacent to the alkynes. Additionally, the terminal alkyne proton resonance appeared as a triplet at δ 1.88 with a small 2.7 Hz coupling constant. The broad resonances of the amide NH and alcohol OH at δ 9.49 and 5.02, respectively were also well defined in the ^{1}H NMR spectrum. Next, a Sonogashira coupling was performed between the

terminal alkyne of **3.71** and iodobenzene employing $Pd(PPh_3)_4$, CuI, and triethylamine. The coupling reaction provided propargyl alcohol **3.72** in an 85% yield. The ^{1}H NMR spectrum of **3.72** showed the disappearance of the terminal alkyne resonance at δ 1.88 along with the appearance of new aromatic multiplets at δ 7.38-7.34 and 7.29-7.24. The ^{1}H NMR spectrum for **3.72** also showed the upfield shifts of the amide and alcohol resonances to δ 7.97 and 3.55, respectively. Finally, reacting propargyl alcohol **3.72** with acetic anhydride, triethylamine, and catalytic DMAP in dichloromethane resulted in acylation of both the alcohol and amide functionality generating diacetate **3.73** in a 98% yield. The ^{1}H NMR spectrum for acetate **3.73** showed the disappearance of both the alcohol and amide proton resonances, as well as the appearance of new acetate methyl singlets at δ 2.70 and 2.10. The ^{13}C NMR spectrum also showed resonances at δ 171.0, 170.6, and 169.0 corresponding to the three carbonyl carbons of **3.73** (Scheme 3.15).



Scheme 3.15 Preparation of Substrate 3.73

It should be noted that in Schemes 3.14 and 3.15 two different methods were used to access propargyl alcohols containing a phenyl-substituted diyne. For the substrates of Scheme 3.14, the lithium acetylide of 1-phenyl-1,6-heptadiyne (**3.53**) was added to protected isatin compounds to yield propargyl alcohols **3.64**, **3.65**, and **3.66**. Preparation of diyne **3.53** followed a

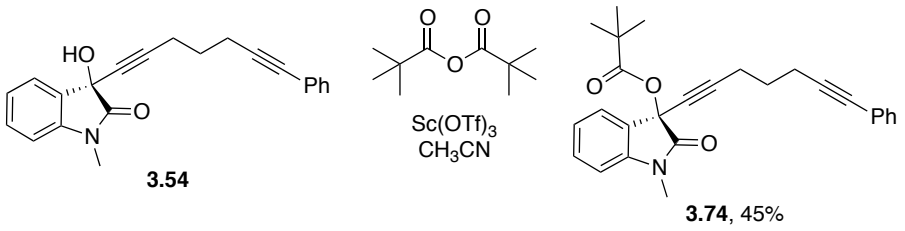
three-step procedure reported by Yamamoto, but was low yielding and difficult to purify.[40] By first adding 1,6-heptadiyne (**3.70**) to the protected isatin, followed by coupling a phenyl group to the terminal alkyne, we were able to prepare propargyl alcohols such as **3.72** in a much more efficient manner.

3.2.4.2 Preparation of Spirooxindole Precursors With Variations at the Ester Group (R^2)

Next, we prepared substrates containing ester groups (R^2) varying from the acetate (Scheme 3.13). This included a bulky pivalic ester **3.74** and a long chain ester **3.75**. A number of factors piqued our interest in varying the ester group. First, it was envisioned that esters other than acetate might have a positive influence on the stability of the [2 + 2] cycloadducts, thus allowing the isolation of the spirooxindole products in higher yields. Second, it is proposed that the propargyl ester undergoes a [3,3]-sigmatropic rearrangement to form an allenyl ester that subsequently participates in the intramolecular [2 + 2] cycloaddition reaction with the tethered alkyne. By employing a bulky ester like pivalic ester, we hypothesized that allene formation could be observed, or even isolation of the allenyl ester may be possible. Finally, varying the ester functionality would potentially allow for their removal under orthogonal reaction conditions. For example, the acetate could be removal under basic conditions, while the pivalate could be removed under acidic conditions.

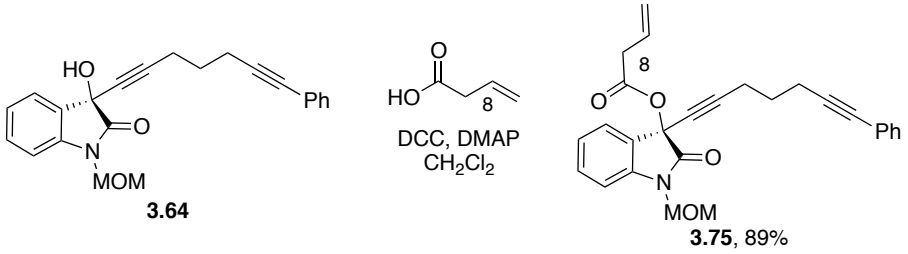
Propargyl pivalate **3.74** was prepared by reacting an acetonitrile solution of propargyl alcohol **3.54** with trimethylacetic anhydride in the presence of a catalytic amount of the Lewis acid scandium triflate. Pivalate **3.74** was isolated in a 45% yield with a majority of the remaining mass being attributed to recovered starting material. The addition of extra trimethylacetic anhydride and scandium triflate, as well as heating, did not encourage the reaction to complete within one day. While an increased reaction time may have provided a higher yield, the reaction

was not further optimized. The formation of propargyl pivalate **3.74** was supported by the disappearance of the –OH proton resonance at δ 3.48 and appearance of a new resonance in the ^{1}H NMR spectrum at δ 1.21, corresponding to the *t*-butyl group of the pivalate (Scheme 3.16).



Scheme 3.16 Preparation of Propargyl Pivalate 3.74

Next, we turned our attention to the preparation of substrate **3.75** containing a long chain ester. To access ester **3.75**, a DCC (*N,N'*-dicyclohexylcarbodiimide) coupling protocol was employed. Propargyl alcohol **3.64**, was reacted with 10-undecenoic acid in the presence of DCC and catalytic DMAP in dichloromethane to provide propargyl ester **3.75** in an 89% yield. Formation of propargyl ester **3.75** was supported by ^{1}H and ^{13}C NMR spectroscopy. Disappearance of the propargyl–OH proton resonance at δ 3.85 was observed in the ^{1}H NMR spectrum. There were also 16 new resonances in the aliphatic region (δ 2.5-1.2), two alkene CH doublet of doublets at δ 5.01 (J = 1.5, 17 Hz) and δ 4.95 (J = 1.5, 10 Hz), and an alkene CH multiplet at δ 5.82 observed in the ^{1}H NMR spectrum. In the ^{13}C NMR spectrum, resonances for the two carbonyl carbons were observed at δ 171.5 and 171.4 (Scheme 3.17).



Scheme 3.17 Preparation of Propargyl Ester 3.75

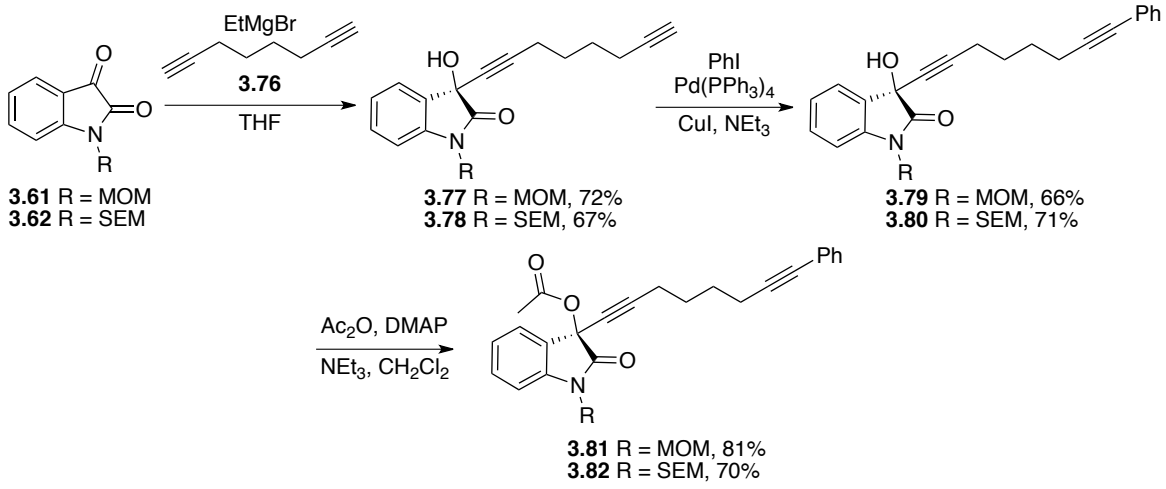
3.2.4.3 Preparation of Spirooxindole Precursors With Variations in Tether Length (n)

Seven membered rings have historically been difficult to access. While a variety of cycloaddition reactions can be applied to form seven membered rings directly, few cycloaddition reactions afford medium sized rings via the tether. Our [2 + 2] cycloaddition methodology has been used to affect the formation of seven membered rings in good yields using tethered allene-ynes. To further explore the generality of the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction in the formation of spirooxindoles, the tether of the diyne was lengthened by one methylene unit to examine the formation of [5.2.0] spirooxindoles.

The preparation of propargyl acetate substrates **3.81** and **3.82** with extended tethers is shown in Scheme 3.18. Preparation of **3.81** initiated with MOM-protected isatin **3.61**, which was added to a pre-prepared Grignard solution of 1,7-octadiyne (**3.83**) in THF at room temperature to provide produce alcohol **3.77** in a 72% yield. Key resonances in the ^{1}H NMR spectrum supporting the formation of **3.77** included two doublets corresponding to the diastereotopic MOM methylene protons at δ 5.15 and 5.10. Additionally, the terminal alkyne proton appeared as a triplet at δ 1.93 with a small 2.4 Hz coupling constant. Next, a Sonogashira coupling was performed between the terminal alkyne of **3.77** and iodobenzene using catalytic $Pd(PPh_3)_4$ and CuI along with triethylamine to afford propargyl alcohol **3.79** in a 66% yield. Key features supporting the formation of **3.79** include the dissappearance of the terminal alkyne triplet at δ 1.93 and the appearance of new aromatic multiplets at δ 7.39 – 7.33 and 7.29 – 7.26 in the ^{1}H NMR spectrum. Also present in the ^{1}H NMR spectrum of **3.79** was the –OH proton resonance at δ 3.13. The last step of the synthetic sequence was acetylation of propargyl alcohol **3.79** utilizing acetic anhydride, triethylamine, and catalytic DMAP in dichloromethane to provide propargyl acetate **3.81** in 81% yield. A key resonance in the ^{1}H NMR spectrum

supporting the formation of **3.81** was the appearance of an acetate singlet at δ 2.10, along with the disappearance of the –OH resonance at δ 3.13 (Scheme 3.18).

Propargyl acetate **3.82** was prepared in an analogous manner to that described for **3.81**. First, the Grignard reagent of 1,7-octadiyne (**3.83**) was formed at room temperature. Subsequent addition of SEM-protected isatin **3.62** produced the propargyl alcohol **3.78** in a 67% yield. The ^{1}H NMR spectrum of **3.78** showed a new triplet at δ 2.29 and a multiplet at δ 2.25-2.20 corresponding to the methylene protons adjacent to the alkynes. The ^{1}H NMR resonances for the two methylene groups in the middle of the tether appeared as a multiplet at δ 1.67-1.63 integrating for four hydrogen. Next, a Sonogashira coupling reaction was performed between the terminal alkyne in **3.78** and iodobenzene using catalytic $Pd(PPh_3)_4$ and CuI along with triethylamine to generate propargyl alcohol **3.80** in a 71% yield. The ^{1}H NMR spectrum of **3.80** showed new aromatic multiplets at δ 7.41-7.38 (2H) and δ 7.30-7.28 (3H). The final step of the sequence was acetylation of propargyl alcohol **3.80** to produce propargyl acetate **3.82** in 70% yield using acetic anhydride, triethylamine and catalytic DMAP (Scheme 3.18).



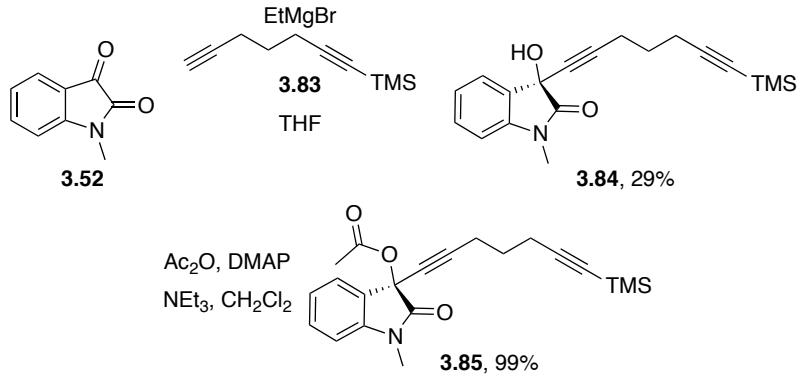
Scheme 3.18 Preparation of Propargyl Acetate 3.81 and 3.82

3.2.4.4 Preparation of Spirooxindole Precursors With Group Variations at the Alkyne Terminus (R^3)

Next, we prepared propargyl acetate substrates varying the substituent (R^3) on the alkyne terminus. Previously, we provided evidence for the allene-yne [2 + 2] cycloaddition reaction proceeding via a biradical intermediate with one of the radicals forming at the distal carbon of the alkyne. It was determined that substituents stabilizing the vinyl radical provided the best yields for the [2 + 2] cycloaddition reaction. Altering the alkyne substituents of the spirooxindole precursors would allow us to further examine whether or not these substituents have an affect on the rate or yield of the reaction. A substrate containing a TMS substituted alkyne was prepared with an eye toward the potential utility of this compound for further transformations subsequent to the [2 + 2] cycloaddition reaction.

Propargyl acetate **3.85** containing a TMS substituted alkyne was the first derivative prepared without phenyl substitution at the alkyne. The reaction sequence to obtain propargyl acetate **3.85** required the synthesis of TMS diyne **3.83** by subjecting 1,7-octadiyne to EtMgBr followed by TMSCl.[83] The reaction to produce diyne **3.83** was low yielding (21%) likely owing to the volatility of this compound; no other products were detected in the reaction. With TMS diyne **3.83** in hand, the lithium acetylide was formed and reacted with *N*-methylisatin (**3.52**) affording the propargyl alcohol **3.84** in a low 29% yield. The low yield was a result of competitive desilylation of product **3.84** during the course of the reaction as supported by ^{1}H NMR spectroscopy. This reaction was only performed once and was not further optimized. The use of a bulky base, such as lithium diisopropylamide, would likely afford propargyl alcohol **3.84** in a higher yield. Key ^{1}H NMR resonances for propargyl alcohol **3.84** included the TMS protons at δ 0.12, as well as the appearance of the oxindole methyl group at δ 3.20. Notable

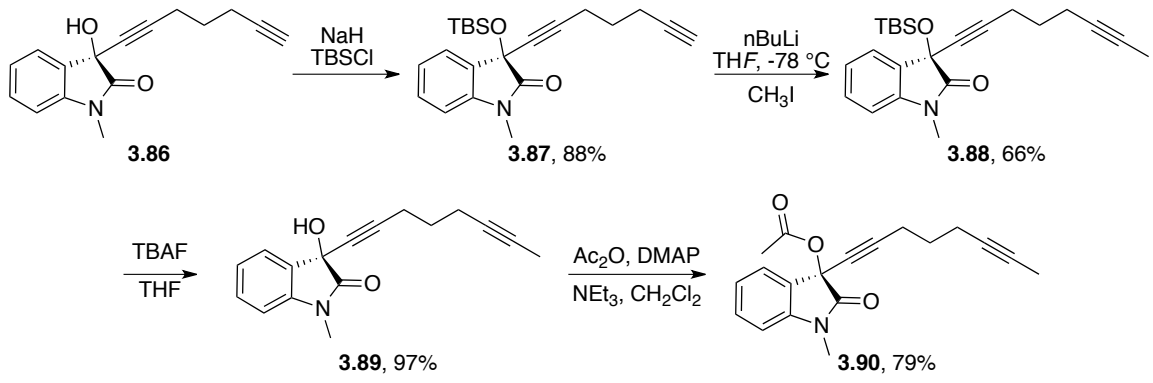
resonances in the ^{13}C NMR spectrum included the alkyne carbons at δ 86.8, 85.2, 77.4, and 69.1, the TMS resonance at δ 0.06, and the quaternary carbon resonance at δ 77.4. Acetylation of propargyl alcohol **3.84** under the previously described acetylation conditions provided propargyl acetate **3.85** in 99% yield. The key resonances supporting the formation of **3.85** included the acetate methyl resonance at δ 2.08 in the ^{1}H NMR spectrum and at δ 20.7 ppm in the ^{13}C NMR spectrum. Additionally, the ^{13}C NMR spectrum indicated two carbonyl resonances corresponding to the oxindole amide and the newly formed acetate at δ 170.8 and 168.5 (Scheme 3.19).



Scheme 3.19 Preparation of Substrate 3.85

In addition to phenyl and TMS substitution at the alkyne terminus of the spirooxindole precursor, a substrate bearing a methyl group at the alkyne terminus was prepared. This propargyl acetate substrate **3.90** was somewhat more laborious to prepare than the other propargyl acetates owing to required alcohol protection and deprotection steps, as shown in Scheme 3.20. Preparation of **3.90** commenced with the TBS protection of propargyl alcohol **3.86** utilizing sodium hydride and *t*-butyldimethylsilyl chloride (TBSCl) to afford TBS propargyl ether **3.87** in 88% yield. Formation of the TBS propargyl ether was supported by ^{1}H NMR spectroscopy with the appearance of atropisomeric TBS methyl resonances at δ 0.29 and 0.17 as well as the TBS *t*-butyl resonance at δ 0.88. Next, we turned our attention to the installation of the methyl group at the alkyne terminus. Deprotonation of alkyne **3.87** using *n*-butyllithium in

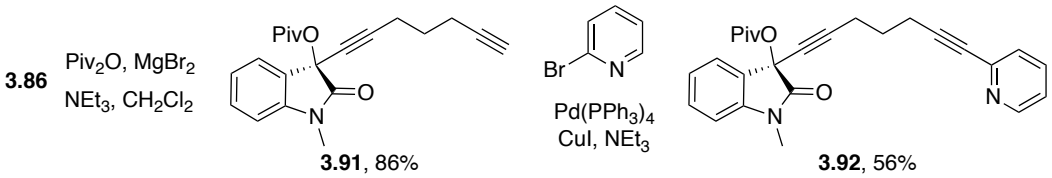
THF at -78 °C, followed by addition of iodomethane generated the methylated alkyne **3.88** in 66% yield. In the ^{1}H NMR spectrum, disappearance of the terminal alkyne resonance at δ 1.93 and the appearance of a methyl triplet at δ 1.75 (*J*=2.4 Hz) were observed. Next, subjecting TBS ether **3.88** to tetrabutylammonium fluoride (TBAF) in THF provided the unprotected propargyl alcohol **3.89** in 97% yield. Disappearance of the TBS resonances at δ 0.88, 0.29, and 0.17, as well as the appearance of a new –OH resonance at δ 3.59 ppm were observed in the ^{1}H NMR spectrum. Direct conversion of propargyl alcohol **3.86** to propargyl alcohol **3.89** was attempted by reacting alcohol **3.86** with 2 equivalents of *n*-butyllithium followed by 1 equivalent of iodomethane, but this reaction provided a complex mixture of products. The protection/methylation/deprotection protocol described above was necessary to obtain compound **3.89**. Finally, propargyl alcohol **3.89** was subjected to acetic anhydride, triethylamine, and catalytic DMAP in dichloromethane to provide the desired propargyl acetate **3.90** in 79% yield. The ^{1}H NMR spectrum of **3.90** showed the appearance of a characteristic acetate –CH_3 resonance at δ 2.07 along with the disappearance of the –OH resonance at δ 3.59. The ^{13}C NMR spectrum showed the expected carbonyl resonances for the amide and acetate at δ 170.9 and 168.6 (Scheme 3.20).



Scheme 3.20 Preparation of Propargyl Acetate 3.90

As a variation on the phenyl moiety, we coupled heteroaromatic rings at the alkyne terminus. Since many biologically valuable compounds owe their properties to hetero-functionality, we aspired to develop a method for the incorporation of additional heteroatoms.

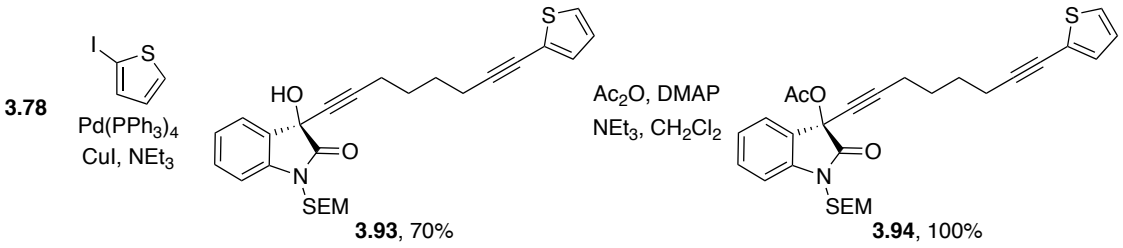
Pivalate **3.92** was the initial substrate prepared with a heteroaromatic ring located on the alkyne terminus. Subjecting propargyl alcohol **3.86** to pivalic anhydride, magnesium bromide, and triethylamine provided propargyl pivalate **3.91** in 86% yield. The key feature in the ^{1}H NMR spectrum supporting the formation of pivalate **3.91** was the new resonance found at δ 1.19 corresponding to the protons of the *t*-butyl moiety. Next, a Sonogashira coupling was performed with alkyne **3.91** and 2-bromopyridine, catalyzed by $Pd(PPh_3)_4$. This reaction provided the desired pyridine substituted alkyne compound **3.92** in a 56% yield. The key attributes supporting the formation of **3.92** included the disappearance of the terminal alkyne resonance at δ 2.03 and the appearance of new aromatic resonances at δ 8.52, 7.60, 7.35-7.32, and 7.18 in the ^{1}H NMR spectrum (Scheme 3.21).



Scheme 3.21 Preparation of Substrate 3.92

The second substrate prepared substituted with a heteroaromatic ring was propargyl acetate **3.94**, which contained a thiophene on the alkyne terminus. Propargyl alcohol **3.78** and 2-iodothiophene were subjected to the Sonogashira conditions described previously to couple the thiophene onto the alkyne terminus to provide propargyl alcohol **3.93** in 70% yield. In the ^{1}H NMR spectrum new aromatic resonances at δ 7.17 (d, J = 4.9 Hz), 7.11 (d, J = 3.5 Hz), and 6.93 (dd, J = 4.9, 4.2 Hz), and an alcohol resonance at δ 3.15 indicated the formation of propargyl

alcohol **3.93**. Next, propargyl alcohol **3.93** was converted to propargyl acetate **3.94** employing acetic anhydride, triethylamine, and catalytic DMAP. The acetylation reaction provided the desired thiophene containing substrate **3.94** in quantitative yield (Scheme 3.22). Formation of **3.94** was supported based on the disappearance of the alcohol resonance, as well as the appearance of a new acetate methyl resonance at δ 2.08 in the ^{1}H NMR spectrum.



Scheme 3.22 Preparation of Thiophene Substituted Substrate 3.94

In summary, a variety of propargyl ester substrates were prepared to examine the scope and limitations of the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction. Figure 3.13 displays these compounds highlighting the various points of diversification. These diversification sites were also chosen based on their potential biological activity. To provide the most versatility we prepared compounds with a MOM **3.67**, SEM **3.68**, Boc **3.69** and acetate **3.73** group substituted on the nitrogen, which could potentially be removed under orthogonal reaction conditions. Three different esters including acetate **3.67**, pivalate **3.74**, and a long chain ester **3.75** were synthesized in order to examine the effect of the ester on the reaction. Substrates with varying tether length, including both 3-carbon **3.67** and 4-carbon **3.81** tethers were also produced. Finally, substrates with various substituents on the alkyne were prepared, including: phenyl, TMS **3.85**, methyl **3.90**, pyridine **3.92**, and thiophene **3.94**. The heterocycles on the terminus of the alkyne are predicted to provide better radical stability to the vinyl radical intermediate, thus increasing the rate of the reaction. In addition, the incorporation of an

additional heterocycle in the cycloadduct may contribute positively to its biological relevance (Figure 3.13).

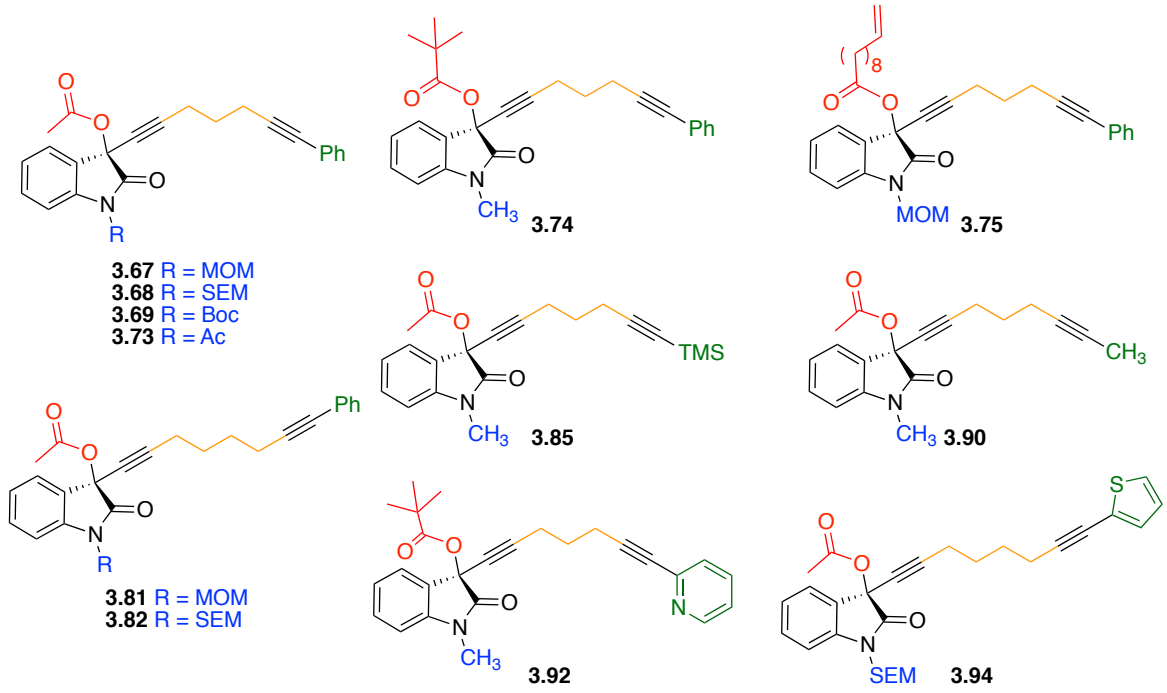


Figure 3.13 Summary of the Spirooxindole Precursors

3.2.5 Synthesis of Spirocyclobutane Oxindoles via Microwave Irradiation of the Propargyl Ester Substrates

Following the synthesis of the propargyl ester substrates, each substrate was subjected to microwave heating, the results of which are detailed below. These reactions were performed using a Biotage Initiator microwave synthesizer in either 0.5-2 mL or 2-5 mL Biotage vials sealed with a Teflon lined crimp cap. The solvents employed were either *N*-methyl-2-pyrrolidinone (NMP) or 1,2-dichlorobenzene (DCB). In only one example benzotrifluoride (BTF) was employed as the reaction solvent, for use in the more powerful Anton-Paar

Monowave microwave synthesizer. The temperatures ranged from 225-250 °C, and the reaction times ranged from 5-90 min.

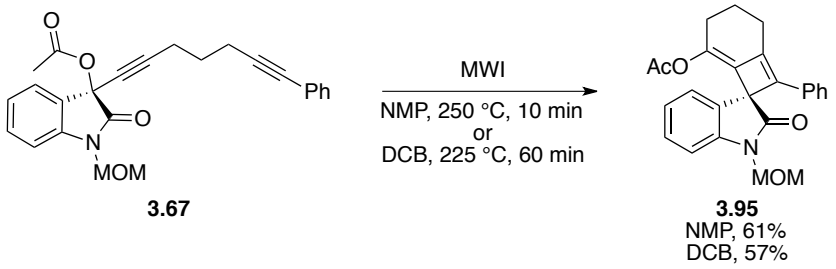
3.2.5.1 Microwave Irradiation of the Spirooxindole Precursors with Variations at the Nitrogen Substituent

Propargyl acetate **3.67**, containing a methoxymethyl (MOM) protected nitrogen, was subjected to microwave irradiation in NMP for 10 min at 250 °C to produce spirocyclobutene oxindole **3.95** in a 61% yield. The ^{1}H NMR spectrum of the spirooxindole product was not incredibly diagnostic, as it appeared similar to that of the starting material spectrum. The most notable change was the resonances for the protons in the tether. In the starting material **3.67**, the methylene protons adjacent to the alkynes appear as triplets at δ 2.48 and 2.44, while the CH_2 protons in the middle of the tether appeared as a quintet at δ 1.82 in the ^{1}H NMR spectrum. Upon cyclization, multiplets with complex splitting patterns for these six protons resulted (δ 2.80-2.67, 2.46-2.33, and 2.18-2.03). The complex splitting was a result of the diastereotopicity of the protons on the cyclohexene ring. This splitting pattern was characteristic of nearly all the spirobicyclo[4.2.0]oxindoles that we have prepared. Also, characteristic in the formation of the spirocyclobutene oxindole compounds was an upfield shift of the acetate CH_3 resonance in the ^{1}H NMR spectrum. In going from propargyl acetate **3.67** to spirooxindole **3.95**, the acetate resonance shifted from δ 2.11 to 1.78. In the ^{13}C NMR of **3.95**, the disappearance of the alkyne resonances at δ 88.8, 88.6, 81.3, and 74.2 was observed. Also, an upfield shift of the quaternary carbon from δ 73.4 to 62.1 was observed in the ^{13}C NMR spectrum for the transformation of propargyl acetate **3.67** to spirooxindole **3.95** (Scheme 3.23).

To examine the solvent effect in the synthesis of spirooxindole **3.95**, DCB was used in addition to NMP. DCB could only be heated to 225 °C in the Biotage 400 W microwave reactor

due to a lower dielectric constant. The benefit to using DCB was that it is removable by column chromatography, whereas NMP must be removed via an aqueous workup. Irradiating propargyl acetate **3.67** for 60 min at 225 °C in DCB provided spirocyclobutane oxindole **3.95** in a 57% yield. This result demonstrated that either DCB or NMP, and likely many other solvents, could be applied without an effect on the reaction yield (Scheme 3.23).

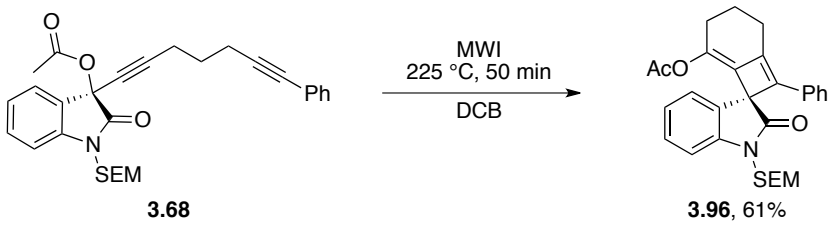
The average yield for this transformation was 60%. While this yield was only moderate, the transformation provided products with a high degree of complexity from simple starting materials. Based on the crude ^{1}H NMR, no other products were formed during the reaction. The loss of mass is currently under investigation is attributed to degradation of the spirooxindole product on silica gel during chromatography. When the reaction was performed in DCB and the solvent was removed *en vacuo* complete recovery of the mass was obtained and based on crude ^{1}H NMR analysis, the product was formed in relatively high purity with only small quantities of impurities. Following silica gel chromatography of the crude material, only a 57% yield of the spirooxindole was obtained.



Scheme 3.23 Microwave Irradiation of Propargyl Acetate 3.67

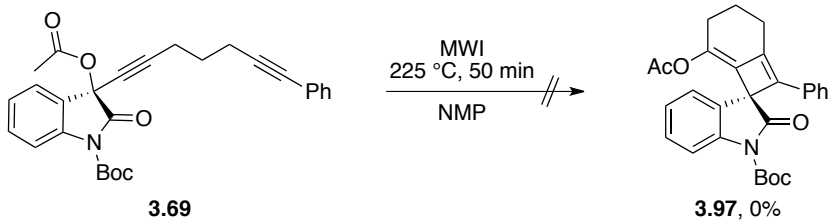
Next, propargyl acetate **3.68**, containing a SEM-protected nitrogen, was irradiated at 225 °C for 50 min in DCB producing spirocyclobutene oxindole **3.96** in 61% yield. The ^{1}H NMR spectrum showed the three characteristic diastereotopic CH_2 multiplets at δ 2.79-2.73, 2.46-2.40, and 2.17-2.07. The ^{13}C NMR spectrum of **3.96** displayed resonances corresponding to the amide

and acetate carbonyls at δ 176.0 and 167.4, while the quaternary carbon appeared as a resonance at δ 62.1 (Scheme 3.24).



Scheme 3.24 Microwave Irradiation of Propargyl Acetate 3.68

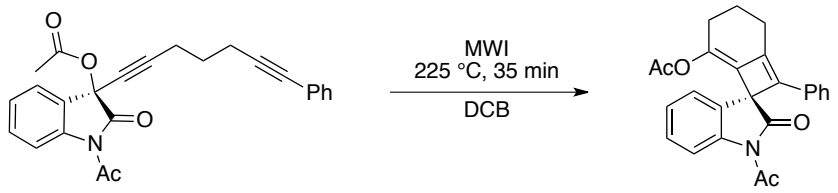
The next substrate examined was propargyl acetate **3.69** containing a Boc protected amide. Irradiating propargyl acetate **3.69** at 225 °C for 50 min in NMP resulted in complete decomposition and no spirooxindole **3.97** was formed. We anticipated that under the reaction conditions, which included heating to a high temperature in a polar solvent, the Boc group might be removed from the oxindole providing an unprotected spirooxindole compound. Unfortunately, the decomposition observed was a result of either an incompatible substrate or an unstable spirooxindole product (Scheme 3.25).



Scheme 3.25 Microwave Irradiation of Propargyl Acetate 3.69

Next, propargyl acetate **3.73** containing an acetyl protected amide was subjected to microwave irradiation for 35 min at 225 °C in DCB to generate spirooxindole **3.98** in a 53% yield. Interestingly, the ^{1}H NMR spectrum of the product did not show diastereotopic splitting for the CH_2 groups of the cyclohexene ring. The allylic CH_2 protons closest to the cyclobutene ring appeared as a distinct triplet at δ 2.37 in the ^{1}H NMR spectrum. Additionally, the

characteristic upfield shift from δ 2.10 to 1.79 of the acetate CH_3 resonance was observed in the ^{1}H NMR spectrum. The most diagnostic features found in the ^{13}C NMR spectrum of spirooxindole **3.98** were the disappearance of the alkyne resonances at δ 90.4, 88.6, 81.5, and 73.9 (Scheme 3.26).

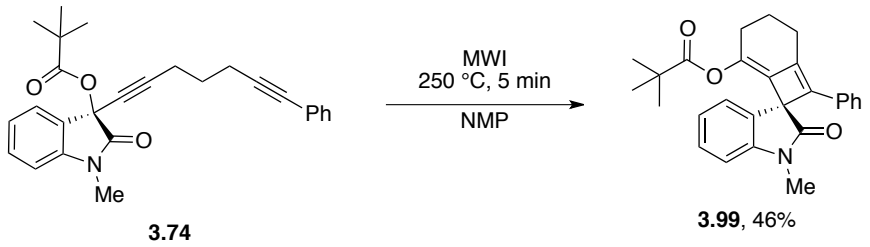


3.73 **3.98**, 53%

Scheme 3.26 Microwave Irradiation of Propargyl Acetate 3.73

3.2.5.2 Microwave Irradiation of the Spirooxindole Precursors with Variations at the Ester Group

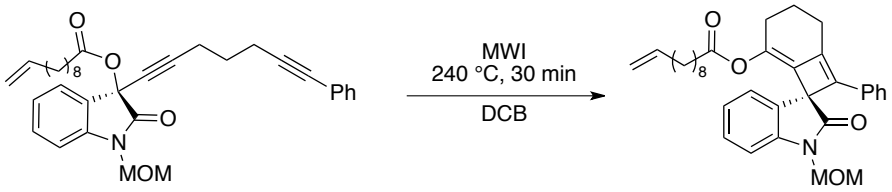
Next, we examined the [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction employing substrates that contained esters other than acetate. Propargyl pivalate **3.74** was subjected to microwave irradiation for 5 min at 250 °C in NMP to generate spirooxindole **3.99** in a 46% yield (Scheme 3.27). The formation of spirooxindole **3.99** was supported based on the appearance of three characteristic methylene multiplets in the ^{1}H NMR spectrum. Additionally, the resonance corresponding to the protons of the pivalate underwent a characteristic upfield shift on formation of **3.99** from δ 1.21 to 0.831 in the ^{1}H NMR spectrum.



3.74 **3.99**, 46%

Scheme 3.27 Microwave Irradiation of Propargyl Pivalate 3.74

In the case of the long chain propargyl ester **3.75**, microwave irradiation at 240 °C for 30 min in DCB produced the spirooxindole **3.100** in a 56% yield. This reaction was performed in an Anton-Paar Monowave microwave synthesizer, which allowed us to heat the reaction in DCB to a higher temperature (240 °C) than what is normally possible. The reaction was not complete by TLC after 10 min, resulting in further irradiation for 20 min to affect complete conversion to spirooxindole **3.100** (Scheme 3.28).



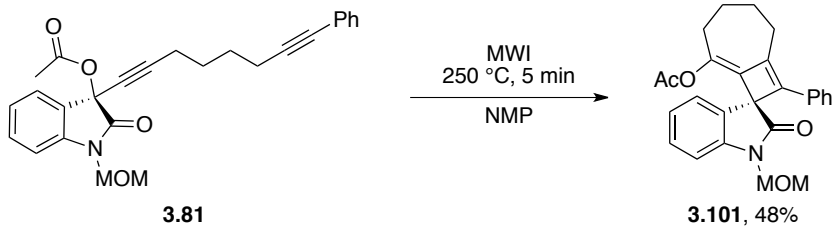
3.75 **3.100**, 56%

Scheme 3.28 Microwave Irradiation of Propargyl Ester 3.75

3.2.5.3 Microwave Irradiation of the Spirooxindole Precursors with Variations in Tether Length (n)

Next, to examine the effect of lengthening the allene-yne tether on the formation of spirooxindoles, propargyl acetate **3.81** was subjected to microwave irradiation for 5 min at 250 °C in NMP. Spirooxindole **3.101** containing the fused seven-membered ring was isolated in a 48% yield. The most notable characteristics in the ^{1}H NMR spectrum of **3.100** were the

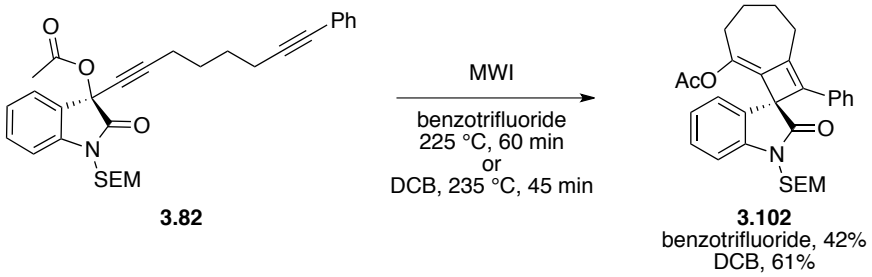
characteristic upfield shift of the acetate CH_3 resonance (δ 2.10 → 1.29) and the diastereotopicity of the CH_2 groups in the seven-membered ring (Scheme 3.29).



3.81 **3.101**, 48%

Scheme 3.29 Microwave Irradiation of Propargyl Ester 3.81

In the case of propargyl acetate **3.82** containing a SEM-protected amide and a four-carbon tether, microwave irradiation for 60 min at 225 °C in benzotrifluoride resulted in formation of the spirooxindole **3.102** in a 42% yield. This experiment made use of an Anton-Paar Monowave instrument in order to superheat the low boiling benzotrifluoride (bp = 102 °C) to 225 °C. The reaction of propargyl acetate **3.82** was also performed using DCB as the solvent (235 °C, 45 min) to produce the spirooxindole **3.102** in a 61% yield. Analysis of the ^{1}H NMR spectrum showed the disappearance of the triplets at δ 2.39 and 2.29 corresponding to the methylene groups adjacent to the alkynes. Appearance of new multiplets, corresponding to the allylic protons in the seven-membered ring, appeared at δ 2.94-2.88, 2.63-2.58, and 2.30-2.26 ppm in the ^{1}H NMR spectrum (Scheme 3.30).

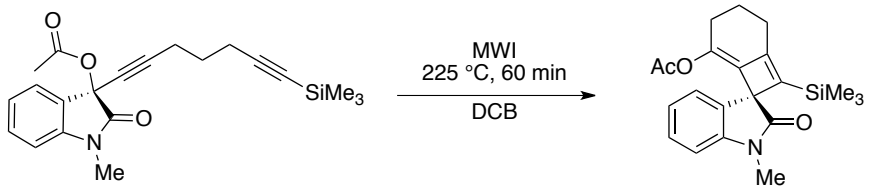


3.82 **3.102**
benzotrifluoride, 42%
DCB, 61%

Scheme 3.30 Microwave Irradiation of Propargyl Ester 3.82

3.2.5.4 Microwave Irradiation of the Spirooxindole Precursors with Variations at the Alkyne Substituent

The study of the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction of substrates with variations on the alkyne substituent commenced with propargyl acetate **3.85** containing a trimethylsilyl (TMS) substituted alkyne. Microwave irradiation of acetate **3.85** in DCB for 60 min at 225 °C resulted in formation of spirooxindole **3.103**, in 50% yield. The ^{13}C NMR spectrum supported the formation of **3.103** by showing the disappearance of the alkyne resonances at 105.9, 88.5, 85.3, and 74.0 ppm. An interesting feature of spirocyclobutene **3.103** was the resonance for the silyl-substituted cyclobutene carbon, which appeared quite far downfield at δ 163.7. In the IR spectrum for spirooxindole **3.103**, a distinct TMS skeletal vibration was observed at 842 cm^{-1} (Scheme 3.31).

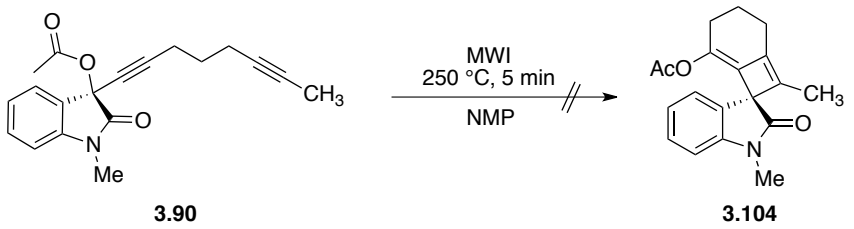


3.85 **3.103**, 50%

Scheme 3.31 Microwave Irradiation of Propargyl Acetate 3.85

Next, propargyl acetate **3.90**, containing a methyl substituted alkyne, was subjected to microwave irradiation for 5 min at 250 °C in NMP. By TLC and ^{1}H NMR spectroscopy the reaction mixture contained a complex mixture of unidentifiable products. Based on ^{1}H NMR spectrum, a trace quantity of spirooxindole **3.104** was formed, which portrayed characteristic features of the spirooxindole products, including an upfield shift of the acetate CH_3 resonance and diastereotopic proton resonances at 1.80-2.50 ppm. Further characterization was not successful due to the limited quantity of isolated product. Based on this result, alkyl groups, such as methyl, on the alkyne terminus do not successfully participate in the tandem [3,3]-sigmatropic

rearrangement/[2 + 2] cycloaddition reaction to form carbocyclic spirooxindoles. The proposed mechanism involves radical formation at the distal alkyne carbon during the [2 + 2] cycloaddition reaction. An alkyl group, such as methyl, will not successfully stabilize the radical and thus proves detrimental to the reaction (Scheme 3.32).

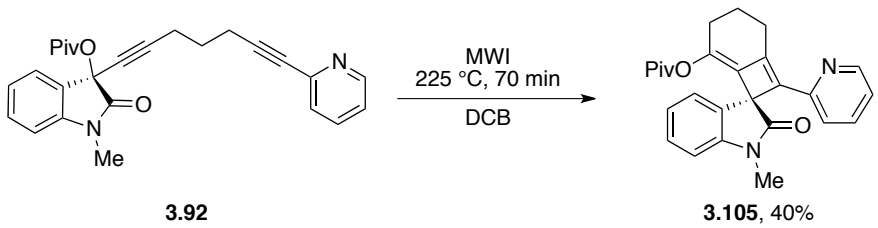


3.90 **3.104**

Scheme 3.32 Microwave Irradiation of Propargyl Acetate 3.90

Next, we investigated the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction with substrates containing a heteroaromatic group appended to the alkyne terminus. These substrates included **3.92**, containing a pyridine, and **3.94**, containing a thiophene. Both of these substituents should successfully stabilize the proposed intermediate diradical, and would also provide interesting spirooxindole products containing an additional heteroatom.

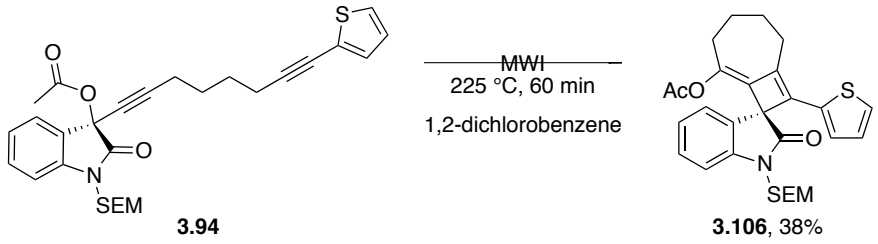
Microwave irradiation of propargyl pivalate **3.92** in DCB for 70 min at 225 °C provided the desired spirooxindole product **3.105** in 40% yield. As was seen for the acetate containing substrates, the pivalate resonance in the ^{1}H NMR experienced an upfield shift from δ 1.19 ppm to 0.83 on transformation of the propargyl pivalate **3.92** to the vinyl pivalate **3.105** (Scheme 3.33).



3.92 **3.105**, 40%

Scheme 3.33 Microwave Irradiation of Propargyl Pivalate 3.92

The final substrate explored was propargyl acetate **3.94**, which contained a thiophene appended at the alkyne terminus. Subjecting this substrate to microwave irradiation for 60 min at 225 °C in DCB generated the desired spirocyclobutene oxindole **3.106** in a 38% yield (Scheme 3.34).



3.94 **3.106**, 38%

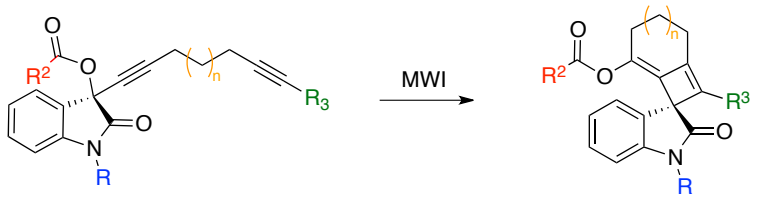
Scheme 3.34 Microwave Irradiation of Propargyl Acetate 3.94

3.2.5.5 Summary

In summary, a plethora of variable propargyl ester substrates were subjected to the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction. The results from irradiating these substrates are summarized in Table 3.3. The substrates possessing Me, MOM, SEM, and Ac as the amide protecting group all underwent the reaction successfully (Table 3.3, Entries 1-5). Variations in the ester moiety seemed to have little effect on the reaction, both the pivalate **3.74** and undecenoate **3.75** substrates produced the spirooxindole products **3.99** and **3.100** in moderate yields (Table 3.3, Entries 6 & 7). Altering the diyne tether length from three carbon atoms to four in substrates **3.81** and **3.82** allowed for the formation of spirocyclobutene oxindole products **3.101** and **3.102** containing a fused seven membered ring (Table 3.3, Entries 8 & 9). Variation of the alkyne substituent also proved successful. Substrate **3.85** containing a TMS substituted alkyne produced spirooxindole **3.103** containing a TMS substituted cyclobutene (Table 3.3, Entry 10). Alkyl groups, such as methyl, appended to the alkyne appeared to have a

negative effect on the reaction and resulted in complete decomposition of the substrate (Table 3.3, Entry 11). This was likely due to the inability of the methyl group to effectively stabilize the proposed radical intermediate formed during the course of the reaction. Finally, when heterocyclic groups, such as pyridine and thiophene were appended to the alkyne terminus, the reaction generated spirooxindoles **3.105** and **3.106** (Table 3.3, Entries 12 & 13). The yields for these transformations are only moderate. Following microwave irradiation, complete mass recovery was obtained after removal of the DCB *in vacuo.* The ^{1}H NMR spectrum of this crude material revealed that the spirooxindole was formed in relatively high purity, and no substantial byproducts were observed. Therefore, we attributed the low yields to decomposition of the spirooxindoles on silica gel during column chromatography. The drop in yield observed for the heteroaromatic substituted compounds **3.105** and **3.106** supported this hypothesis. These spirooxindoles are more polar and thus spent more time on the silica gel during purification, which resulted in a greater degree of decomposition.

Table 3.3 Spirooxindole Products Formed Upon Microwave Irradiation of the Propargyl Ester Substrates



	Substrate	R	R^2	R^3	n	Solvent	Temp[a]	Time	Product
1	3.67	MOM	Ac[b]	Ph	1	NMP[c]	250	10 min	**3.95** 61%
2	3.67	MOM	Ac	Ph	1	DCB[d]	225	60 min	**3.95** 57%
3	3.68	SEM	Ac	Ph	1	DCB	225	60 min	**3.96** 61%
4	3.69	Boc	Ac	Ph	1	NMP	225	50 min	**3.97** 0%[e]
5	3.73	Ac	Ac	Ph	1	DCB	225	35 min	**3.98** 53%
6	3.74	Me	Piv[f]	Ph	1	NMP	250	5 min	**3.99** 46%
7	3.75	MOM	Und[g]	Ph	1	DCB	240	30 min	**3.100** 56%
8	3.81	MOM	Ac	Ph	2	NMP	250	5 min	**3.101** 48%
9	3.82	SEM	Ac	Ph	2	BTF[h]	225	60 min	**3.102** 42%
10	3.85	Me	Ac	TMS	1	DCB	225	60 min	**3.103** 50%
11	3.90	Me	Ac	Me	1	NMP	250	5 min	**3.104** 0%
12	3.92	Me	Piv	Pyr[i]	1	DCB	225	70 min	**3.105** 40%
13	3.94	SEM	Ac	Thi[j]	2	DCB	225	60 min	**3.106** 38%

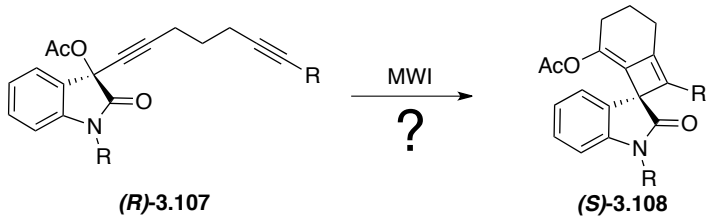
[a]Temperature is reported in °C; [b]Ac corresponds to acetyl; [c]NMP = *N*-methyl-2-pyrrolidinone; [d]DCB = 1,2-dichlorobenzene; [e]Complete decomposition of the reaction was observed; [f]Piv corresponds to pivaloyl; [g]Und corresponds to 10-undecenoate; [h]BTF = benzotrifluoride; [i]Pyr = 2-pyridine substitution; [j]Thi = 2-thiophene substitution

3.3 EXAMINING CHIRAL TRANSFER IN THE TANDEM [3,3]-SIGMATROPIC REARRANGEMENT/[2 + 2] CYCLOADDITION REACTION

3.3.1 Introduction

With a diverse set of spirooxindole substrates in hand, our next objective was to investigate chiral transfer in the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction. In short, if a chiral non-racemic propargyl acetate ***(R)*-3.107** were subjected to the reaction conditions, would a chiral non-racemic spirooxindole ***(S)*-3.108** result (Scheme 3.35)? It should

be noted that the compounds described in the following sections are given *R* or *S* configurations based on the way they are drawn. While the enantiopurity of every chiral non-racemic compound that we prepared was measured, the absolute configurations were not determined. For the purpose of this text, the *R* and *S* designations should only be considered a bookkeeping tool.



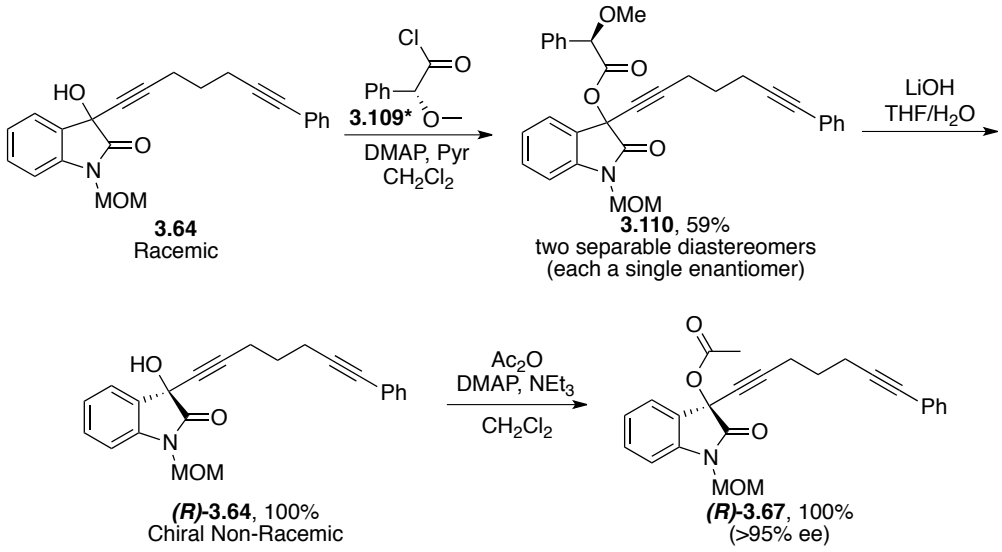
***(R)*-3.107** **(S)-3.108**

Scheme 3.35 Hypothesized Chiral Transfer from a Propargyl Acetate to a Spirooxindole

3.3.2 Preliminary Experiment Using a Chiral, Non-Racemic Propargyl Acetate

To investigate the transfer of chirality, we prepared a chiral non-racemic propargyl acetate. Beginning with racemic propargyl alcohol **3.64**, an esterification was performed using acid chloride ***(R)*-3.109**, DMAP, and pyridine to produce propargyl ester **3.110** in a 59% yield as a separable 1.4:1 mixture of diastereomers, each as a single enantiomer. The diastereomers were each isolated and characterized. The less polar diastereomer was carried through the remainder of the reaction sequence. Key ^{1}H NMR characteristics supporting the formation of ester ***(R)*-3.110** included the loss of the –OH resonance at 3.85 ppm, the appearance of a new resonance at 4.81 ppm corresponding to the proton alpha to the ester carbonyl, and the appearance of a new resonance at 3.40 ppm corresponding to the newly incorporated methoxy group. The less polar diastereomer of ester ***(R)*-3.110** was then saponified using lithium hydroxide in THF and water to generate propargyl alcohol ***(R)*-3.64** as a single enantiomer in quantitative yield. The ^{1}H and ^{13}C NMR spectra of enantiopure ***(R)*-3.64** matches the NMR spectra of racemic **3.64**. Acetylation of

propargyl alcohol ***(R)*-3.64** using acetic anhydride, catalytic DMAP, and triethylamine provided the propargyl acetate ***(R)*-3.67** in quantitative yield as a single enantiomer. The NMR spectrum for enantiopure acetate ***(R)*-3.76** was found to match that of the racemic compound (Scheme 3.36).



Scheme 3.36 Preparation of Chiral, Non-Racemic Acetate (R)-3.67

In order to ensure that we had obtained a single enantiomer of the propargyl acetate ***(R)*-3.67**, a chiral lanthanide shift NMR experiment was performed as shown in Figure 3.14. This technique requires sequential addition of a chiral europium species to a known amount of the racemic compound. During addition, NMR distinguishable diastereomeric complexes are produced. If too little shift reagent is added, the enantiomers cannot be distinguished, but if too much is added, the NMR becomes too disordered to distinguish the various protons. When the appropriate amount of shift reagent has been determined, attention can be directed toward the enantioenriched compound. By adding the predetermined amount of chiral europium complex to a known amount of enantioenriched compound, the two-diastereomeric complexes will be

distinguishable in the ^{1}H NMR spectrum. Based on integration values, the enantiomeric excesses can be calculated with an error of *ca.* 5%.

Following the protocol above, racemic acetate **3.67** required 0.25 equiv. of (+)-Eu(hfc)$_3$ to distinguish between the diastereomeric complexes. The proton at C-4 of the oxindole displayed the best resolution (H_a in Figure 3.14). A single diastereomeric complex was observed in the ^{1}H NMR spectrum after subjecting the enantiopure acetate ***(R)*-3.67** to 0.25 equiv. of (+)-Eu(hfc)$_3$, which corresponded to >95% enantiomeric excess (Figure 3.14).

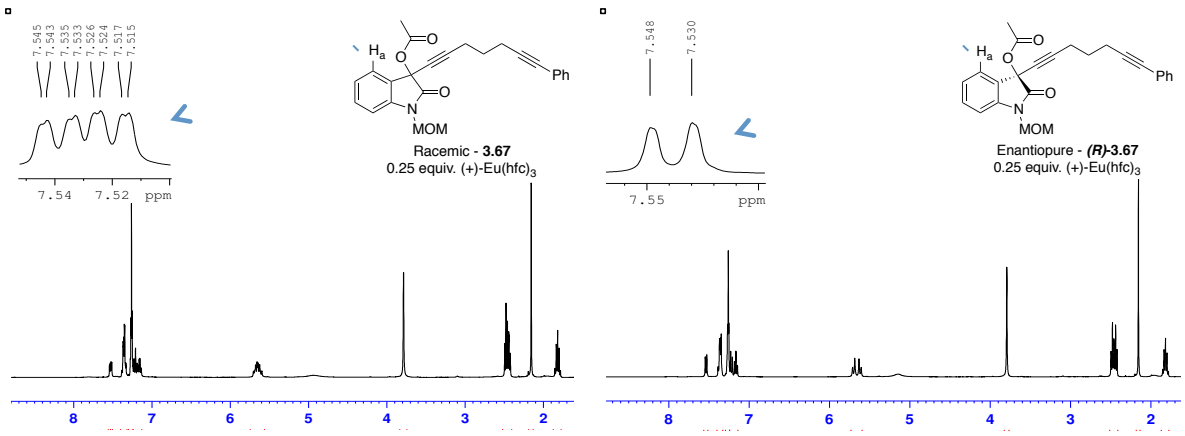
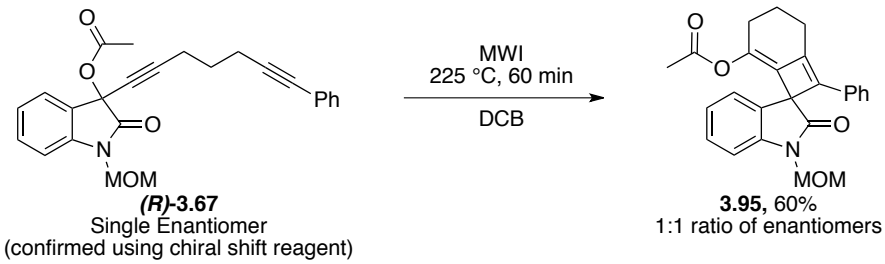


Figure 3.14 Chiral Shift ^{1}H NMR Spectrum of Racemic and Enantiopure 3.67

With enantiopure propargyl acetate ***(R)*-3.67** in hand, we were poised to subject it to the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction. Propargyl acetate ***(R)*-3.67** was irradiated at 225 °C for 60 min in DCB, and the spirooxindole **3.95** was isolated in a 60% yield (Scheme 3.37). The enantioselectivity was determined by chiral lanthanide shift NMR analysis utilizing (+)-Eu(hfc)$_3$. NMR analysis indicated complete racemization during the course of the reaction. Figure 3.15 shows the NMR spectrum of the spirooxindole **3.95** obtained from both the racemic acetate **3.67** as well as the enantiopure acetate ***(R)*-3.67**.



***(R)*-3.67**
Single Enantiomer
(confirmed using chiral shift reagent)

3.95, 60%
1:1 ratio of enantiomers

Scheme 3.37 Microwave Irradiation of Enantiopure Propargyl Acetate *(R)*-3.67

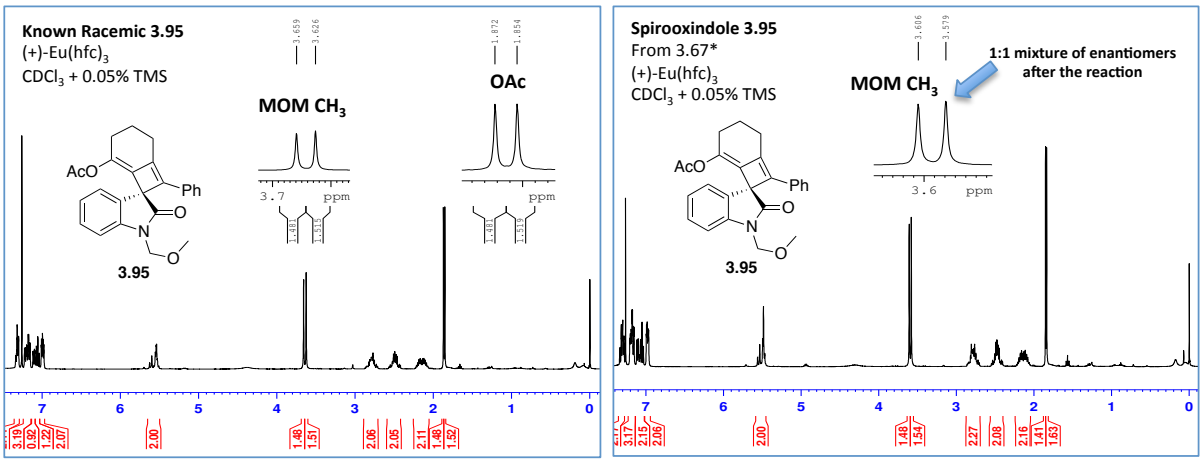
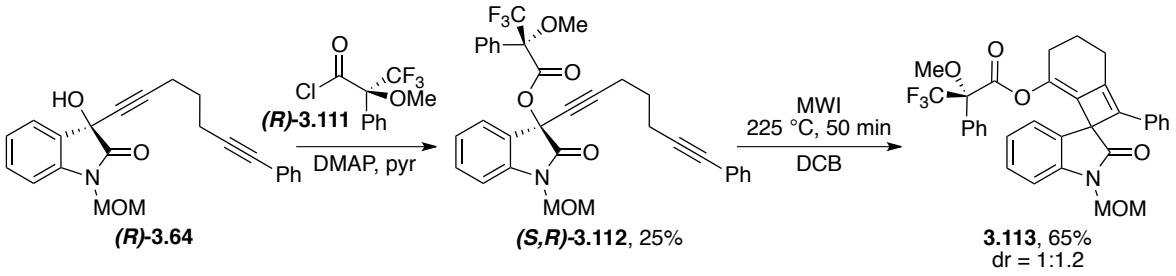


Figure 3.15 Chiral Lanthanide Shift NMR Analysis of Spirooxindole 3.95

3.3.3 Follow Up Experiment Using a Mosher Ester

An additional experiment to examine chiral transfer in the synthesis of spirocyclobutene oxindoles is shown in Scheme 3.38. Beginning with enantiopure ***(R)*-3.64**, the Mosher ester was prepared using Mosher acid chloride ***(R)*-3.111** to provide ester ***(S,R)*-3.112** as a single enantiomer. Key features of the ^{1}H NMR supporting the formation of ester ***(S,R)*-3.112** included the disappearance of the –OH resonance at δ 3.85, as well as the appearance of a resonance at δ 3.58 corresponding to the methoxy group on the Mosher ester. Propargyl ester ***(S,R)*-3.112** was then irradiated at 225 °C for 50 min in DCB to provide spirooxindole **3.113** in a 65% yield as a

1:1.2 ratio of diastereomers based on ^{1}H NMR spectroscopy. In order to obtain a mixture of diastereomers in this reaction, the stereocenter at C-3 of ***(S,R)*-3.112** must have scrambled during the course of the reaction (Scheme 3.38). Figure 3.16 shows the NMR spectrum of the starting material ***(S,R)*-3.112** and crude product **3.113**.



Scheme 3.38 Preparation and Microwave Irradiation of Ester *(S,R)*-3.112

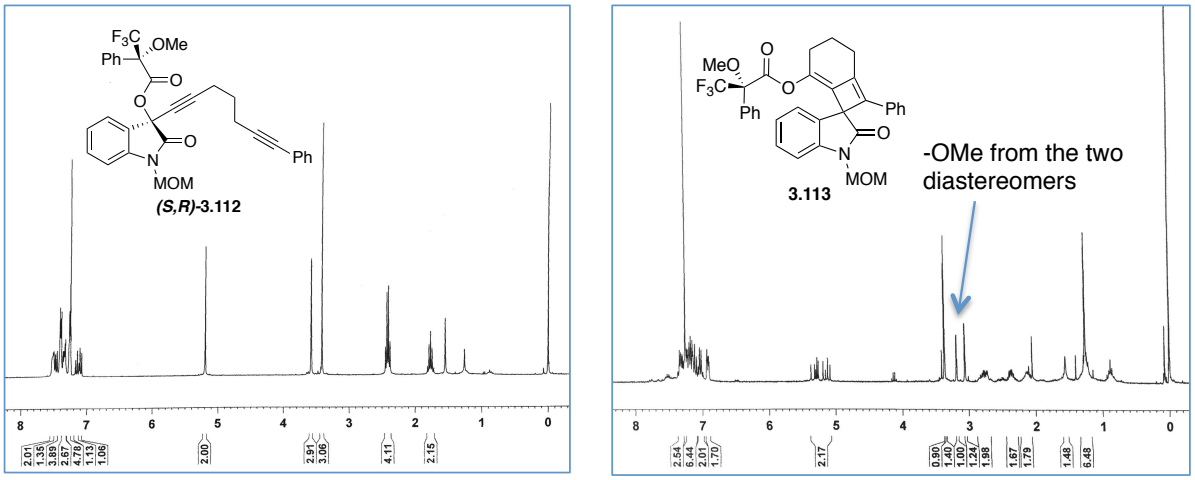
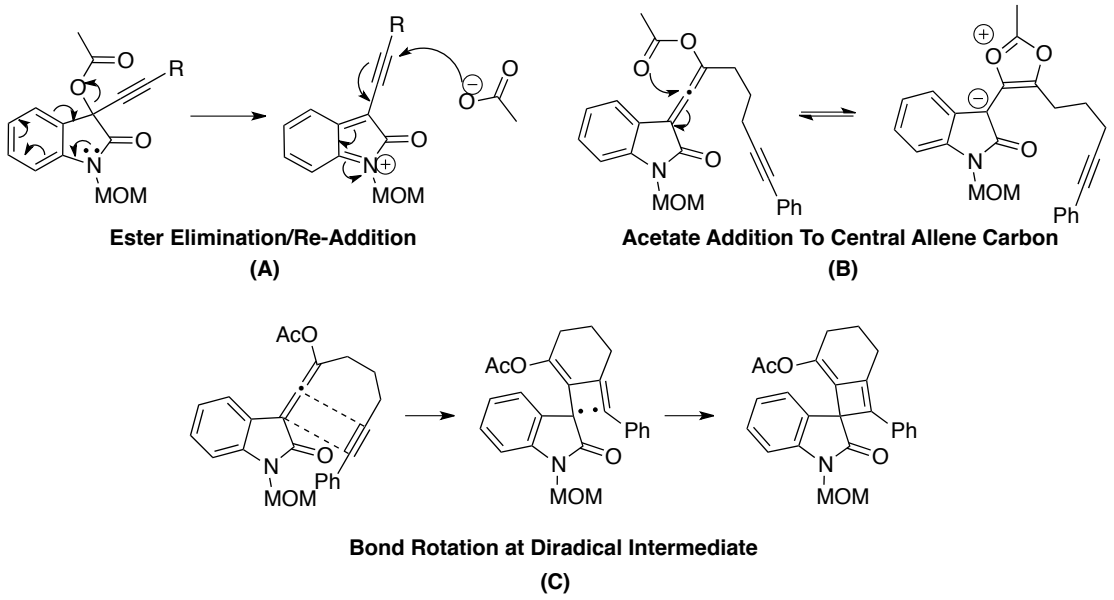


Figure 3.16 NMR of Spirooxindole 3.113 Showing Diastereomeric Products

3.3.4 Mechanistic Hypotheses for Racemization in the Spirooxindole Products

Based on the results described in Schemes 3.37 and 3.38, the tandem [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition reaction does not proceed with transfer of chiral information, and the stereocenter at C-3 is scrambled during the reaction. To investigate the

source of racemization, three mechanistic hypotheses were proposed, as shown in Scheme 3.39. First, in the elimination/re-addition mechanism, allene formation does not occur via a sigmatropic rearrangement; rather, the acetate is initially eliminated through nitrogen lone pair participation to form the intermediate iminium ion. The free acetate can then attack at the alkyne, resulting in allene formation and rearomatization of the substrate. Under the high temperatures required for the reaction, aromaticity can be broken forming an sp^2-hybridized carbon at C-3, which would result in the observed scrambling of the stereocenter (Scheme 3.39A). The second potential pathway for racemization involves initial formation of the allenyl acetate intermediate, followed by addition of the carbonyl oxygen into the central carbon of the allene to produce the zwitterionic complex as shown in Scheme 3.39B. If this complex were formed, bond rotation around the single bond at C-3 would result in loss of enantiopurity. While this mechanism may be unlikely, especially in a non-polar solvent such as DCB, it was still considered (Scheme 3.39B). The final mechanistic possibilty for racemization that we contemplated involves a diradical intermediate resulting during the [2 + 2] cycloaddition (see Ch. 2 for a full discussion of the diradical intermediate). Although the diradical is presumed to be short lived, there is the potential for bond rotation occurring before ring closure to form the four-membered ring, which would account for the observed racemization if the reaction proceeds by a diradical pathway (Scheme 3.39C).

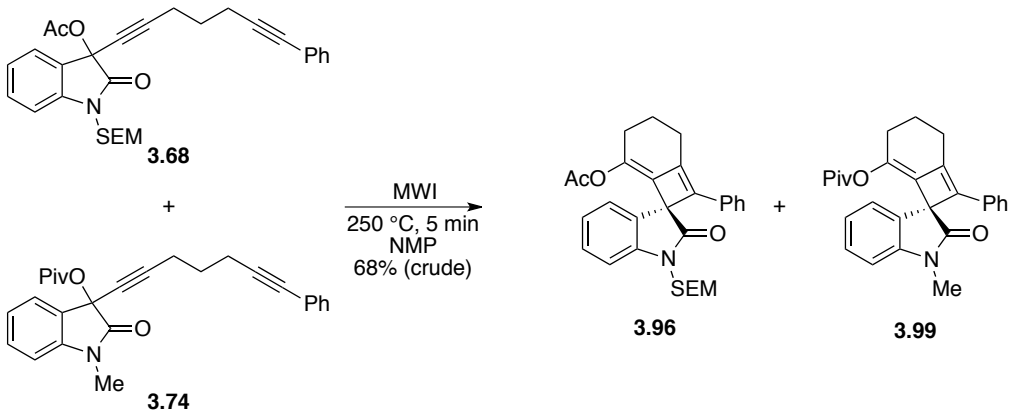


Scheme 3.39 Mechanistic Hypotheses for the Observed Racemization in the Spirooxindole Products

3.3.5 Investigating the Racemization Mechanism Using a Crossover Experiment

To pinpoint the exact source of racemization, we investigated each of the three mechanisms shown in Scheme 3.39. To examine the validity of the proposed elimination/re-addition (Scheme 3.39A) a crossover experiment was conducted. Two propargyl acetate substrates **3.68** and **3.74** were selected. Substrate **3.68** contained a propargyl acetate and SEM-protected amide. Substrate **3.74** contained a propargyl pivalate and a methyl-protected amide. The two substrates were mixed and subjected to the standard reaction conditions. If ester elimination/re-addition is occurring, four different spirooxindole products should result; if this mechanism is not operative, then only two products will be observed. Analysis of the reaction mixture revealed only two spirooxindole products, thus providing support that elimination/re-addition was not the operative mechanism for racemization. Additionally, the reaction was

performed in a polar solvent (NMP) in an effort to prevent any effect from tight-ion pairing (Scheme 3.40).



Scheme 3.40 Crossover Experiment

Figure 3.17 shows the ^{1}H NMR spectrum from the crossover experiment. The two spirooxindole products can be easily distinguished and the major resonances are assigned. The key ^{1}H NMR resonances supporting the formation of spirooxindole **3.96** include the TMS singlet at -0.05 ppm (H_A), and the acetate singlet at 1.76 ppm(H_H). The key ^{1}H NMR resonances for spirooxindole **3.99** include the pivalate at 0.83 ppm (H_e) and the *N*-CH_3 at 3.33 ppm (H_a). The two products resulting from crossover were determined as absent from the reaction based on the lack of characteristic resonances that would have otherwise been present in the ^{1}H NMR spectrum (Figure 3.17).

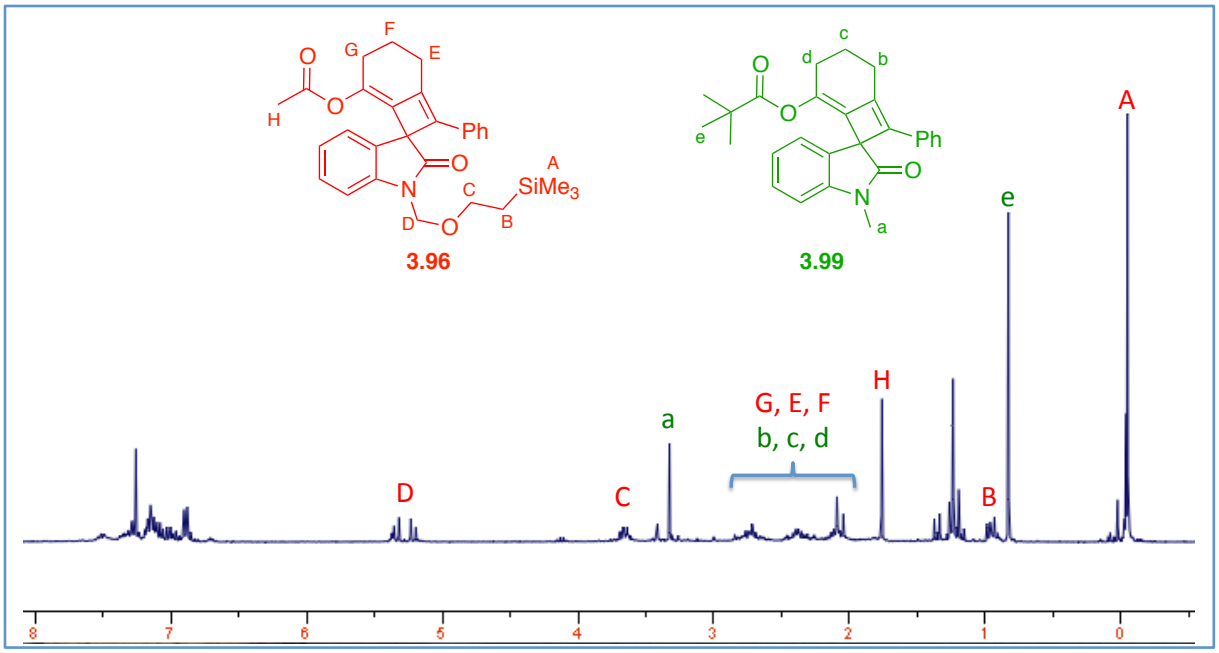


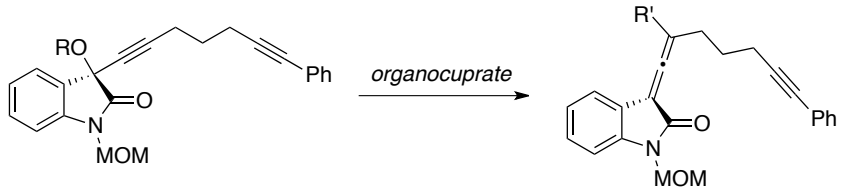
Figure 3.17 Crossover Experiment NMR Spectrum

3.3.6 Investigating the Mechanism of Racemization by Preparing an Allenyl Oxindole Deficient of the Acetate Moiety

In order to examine the proposed zwitterionic mechanism (Scheme 3.39B), we prepared a 3-allenyl oxindole deficient of the acetate moiety. Having propargyl acetate ***(R)*-3.67** as a single enantiomer, we turned our attention to S_N2' displacement of the propargyl acetate using cuprate chemistry to provide an enantioenriched allene ***(R)*-3.114**. It has previously been reported that delivery of an alkyl group from an organocuprate in an S_N2' manner occurs with retention of stereochemical information in the resulting allene.[75] Based on these results, we began to explore various conditions to generate the desired 3-allenyloxindole ***(R)*-3.114**. As discussed previously, 3-allenyl oxindoles are extremely rare, likely owing to their high reactivity. This made generation of ***(R)*-3.114** quite challenging. To affect the cuprate reaction, various leaving groups (OMs, OMe, OAc), solvents (THF, Et_2O), and cuprates (lower and higher order cyanocuprates)

were investigated. The reaction using a mesylate was problematic due to the instability of the mesityl substrate, even at low temperatures (Table 3.4, entry 1). The more stable substrates substituted with an –OMe or –OAc were completely unreactive toward the lower order cuprates (Table 3.4, entries 2-4). The optimal conditions were discovered employing the higher order cyanocuprate *t*-$Bu_2Cu(CN)Li_2$ with the propargyl acetate substrate. These conditions led to formation of the desired allenyl oxindole ***(R)*-3.114** in 49% yield. The low yield was due to subsequent addition of the *t*-butyl cuprate into the central carbon of the newly formed allene product ***(R)*-3.114**, providing a di-*t*-butyl oxindole compound. Formation of allenyloxindole ***(R)*-3.114** was supported by the disappearance of the acetate $-CH_3$ resonance at δ 2.11 and the appearance of a new *t*-butyl resonance at δ 1.22 in the ^1H NMR spectrum. Additionally, the ^{13}C NMR spectrum showed the disappearance of the acetate carbonyl resonance at δ 168.5 and the appearance of a characteristic central allene carbon resonance at δ 203.4. The IR spectrum of ***(R)*-3.114** showed a distinct allene stretch at 1945 cm^{-1}.

Table 3.4 Screening Conditions for Formation of Allenyl Oxindole *(R)*-3.114



***(R)*-3.67** ***(R)*-3.114**

Entry	R	Solvent	Temp	Cuprate	R'	Yield
1	Ms	THF	-45 °C	MeCu(CN)Li	Me	0%[a]
2	Me	Et_2O	0 to 35 °C	MeCu(CN)Li	Me	0%[b]
3	Ac	Et_2O	0 °C	MeCu(CN)Li	Me	0%[b]
4	Ac	THF	-78 °C to rt	MeCu(CN)Li	Me	0%[c]
5	Ac	Et_2O	-78 °C	*t*-BuCu(CN)Li	*t*-Bu	0%[b]
6	Ac	THF	-78 °C	*t*-$Bu_2Cu(CN)Li_2$	*t*-Bu	49%[d]

[a]Complete decomposition of the mesylate (generated in situ) was observed prior to cuprate addition. [b]Complete recovery of starting material. [c]Starting material was recovered in addition to the deacylation product. [d]Also isolated in 21% yield was the product of a second addition of the tert-butyl group to the central carbon of the allene.

To examine the transfer of chirality from propargyl acetate ***(R)*-3.67** to allene ***(R)*-3.114**, a chiral lanthanide NMR shift analysis was conducted using (+)-Eu(hfc)$_3$. The results are shown in Figure 3.18. For racemic **3.114**, the *t*-butyl resonances of the diastereomeric complexes were split into two distinct singlets at δ 1.23 and 1.20. Enantiomerically enriched ***(R)*-3.114** showed a lone singlet at δ 1.22 indicating a single diastereomeric complex, and thus a single enantiomer. Based on this analysis, the chiral allene was formed in >95% enantiomeric excess (Figure 3.18).

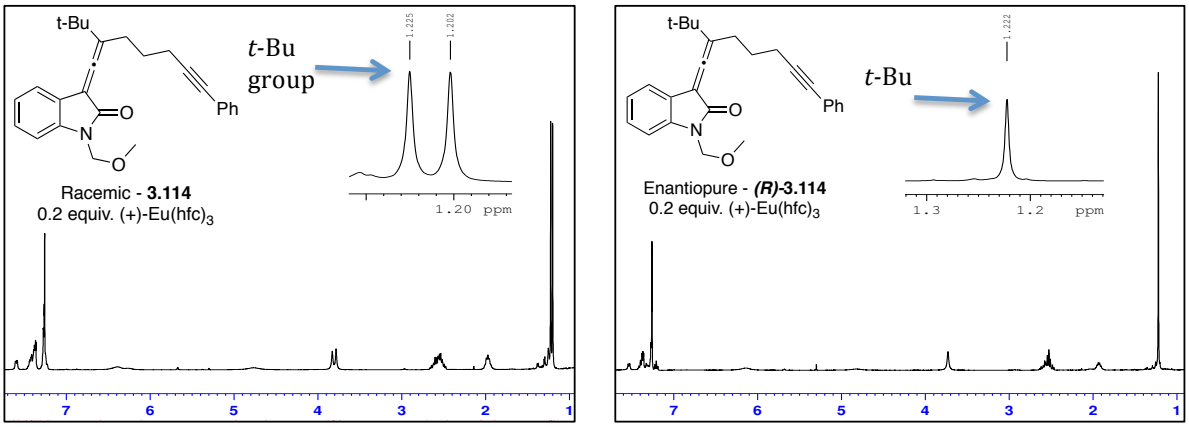
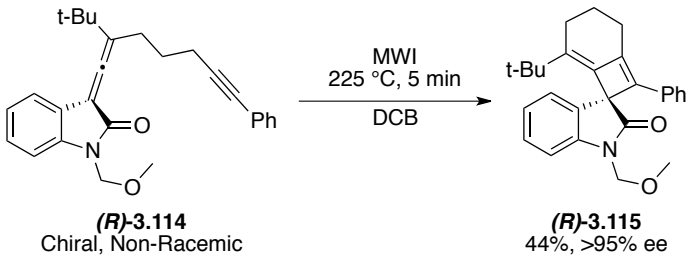


Figure 3.18 Chiral Shift NMR Analysis of Racemic and Enantiopure 3.114

3.3.7 Complete Chiral Transfer in the Thermal Intramolecular [2 + 2] Cycloaddition Reaction of Allene-ynes to Form a Chiral Non-Racemic Spirooxindole

With enantioenriched allenyl oxindole ***(R)*-3.114** in hand, we were poised to subject it to the [2 + 2] reaction conditions to observe if chirality is transferred to the spirooxindole product. Allene-yne ***(R)*-3.114** was irradiated in the microwave for 5 min at 225 °C in DCB. The reaction provided spirooxindole ***(R)*-3.115** in 44% yield (Scheme 3.41). The ^{1}H NMR spectrum of the product ***(R)*-3.115** was not very diagnostic as it shared many characteristics with the ^{1}H NMR spectrum of the starting material ***(R)*-3.114**. In the ^{13}C NMR spectrum, disappearance of the

central allene carbon resonance at δ 204.3 and the alkyne carbon resonances at δ 81.2 and 89.4 were observed. Additionally, the appearance of a new quaternary carbon resonance at δ 77.2 was observed in the ^{13}C NMR spectrum.



***(R)*-3.114**
Chiral, Non-Racemic

***(R)*-3.115**
44%, >95% ee

Scheme 3.41 Formation of a Chiral Non-Racemic Spirooxindole

Chiral NMR shift analysis of ***(R)*-3.115** was performed using (+)-Eu(hfc)$_3$. When racemic **3.115** was treated with 0.75 equiv. of the shift reagent, singlets at 3.98 and 3.87 ppm were observed, which corresponded to methyl of the MOM moiety in the diastereomeric complexes. When spirooxindole ***(R)*-3.115**, obtained from the [2 + 2] cycloaddition of enantioenriched ***(R)*-3.114**, was subjected to the chiral NMR shift analysis, a lone resonance at 4.05 ppm was observed. Based on the NMR shift analysis, the spirooxindole product ***(R)*-3.115** was formed in >95% enantiomeric excess (Figure 3.19).

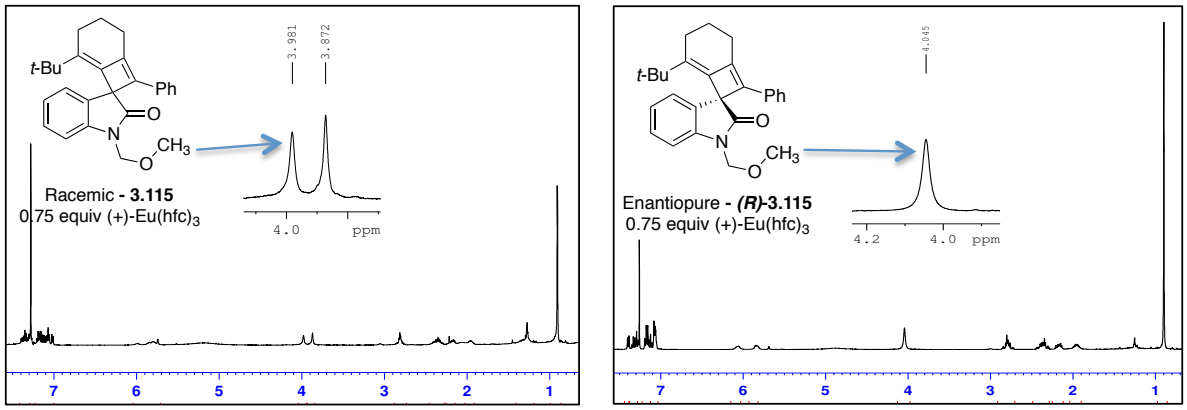
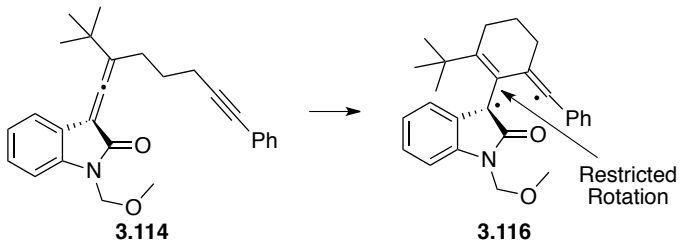


Figure 3.19 Chiral Shift ^1H NMR Spectrum of Racemic and Enantiopure 3.115

Based on this result we are left with two mechanistic possibilities for the observed racemization when employing propargyl acetate ***(R)*-3.67**. The zwitterionic pathway in Scheme 3.39b could be operative, and acetate addition into the central carbon of the allene is the cause of racemization. Thus, when utilizing a substrate devoid of the acetate, complete transfer of chiral information occurs. At this point, the diradical mechanism for racemization can still be functional. If racemization occurs via rotation at the diradical intermediate, hindered rotation may allow for increased enantioselectivity in the reaction as depicted in Scheme 3.42. The bulk of the *t*-butyl group could restrict rotation around the single bond due to steric interactions between it and the oxindole moiety.



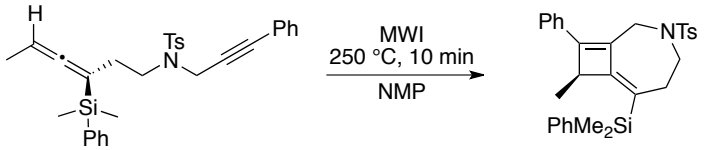
3.114 **3.116**

Scheme 3.42 Postulated Chiral Transfer Due to Restricted Rotation

3.3.8 Examining Chiral Transfer Using a Simple Allene-yne Substrate

The reaction described in Scheme 3.42 relies on steric interactions between the bulky *t*-butyl group and oxindole to prevent bond rotation and provide high enantioselectivity. In order to further investigate this hypothesis, examined a substrate that still contained a fairly bulky allene substituent, but without the presence of the bulky oxindole. Allene-yne ***(R)*-3.117** was selected because it had previously been prepared enantioselectively in our group. This allene-yne was prepared in 93% enantiomeric excess (HPLC, determined by ChiralTech Inc.) and contained a bulky dimethylphenylsilicon appended to the allene, making it an ideal substrate for examining

chiral transfer. Microwave irradiation of ***(R)*-3.117** provided the [2 + 2] adduct ***(S)*-3.118** in a 93% yield and 54% ee (determined by HPLC using a chiral OD column). These results show erosion of the enantiomeric purity, but not complete racemization, suggesting that the bulk of the silicon group helped maintains some enantioselectivity, but there was not enough steric bulk to obtain complete chiral transfer. In the ^{1}H NMR spectrum, an upfield shift of the allene proton from 4.88 ppm to 3.35 ppm was observed upon transformation from ***(R)*-3.117** to ***(S)*-3.118**. There was also an upfield shift observed for the allene methyl group, from 1.62 ppm to 1.11 ppm, upon conversion to the cyclobutane methyl. Distinct diastereotopic doublets at δ 4.54 (17.4 Hz) and δ 4.10, (16.5 Hz) were observed for the methylene protons on the carbon atom between the cyclobutene and nitrogen. This diastereotopicity is characteristic of the cyclization products (Scheme 3.43).



***(R)*-3.117**
93% ee

***(S)*-3.118**
93%, 54% ee

Scheme 3.43 A [2 + 2] Cycloaddition Reaction using Enantioenriched 3.117

3.3.9 Summary

In summary, the mechanism for racemization observed in the conversion of propargyl acetates to spirooxindoles was investigated using a variety of methods. During our investigation, we discovered that by using a *t*-butylallenyl oxindole, a chiral non-racemic spirocyclobutene oxindole product could be prepared. This was quite an interesting result, as there are no reports in the literature of enantioselective thermal allene-yne [2 + 2] cycloadditions where there is

complete transfer of chirality from the allene precursor to the alkylidene cyclobutene product. Based on the results discussed, our working hypothesis is that racemization occurs via bond rotation at the intermediate diradical. By adding steric bulk to the allene-yne substrate, rotation can be restricted and lead to complete transfer of chirality in the thermal allene-yne [2 + 2] cycloaddition. Additional experiments could be performed to further examine the mechanism and definitively pinpoint the cause for racemization or chiral transfer depending on the substrate. This would include preparing an enantioenriched 3-allenyloxindole that contains a hydrogen in place of the *t*-buty group. If a deterioration of enantiomeric excess were observed in this substrate on conversion to the spirooxindole, then this would provide additional evidence for the biradical intermediate.

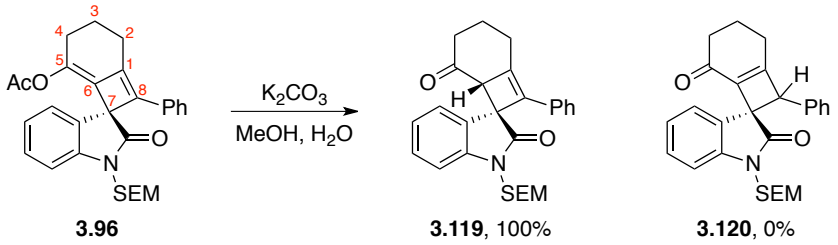
3.4 SUBSEQUENT TRANSFORMATIONS OF THE SPIROCYCLOBUTANE OXINDOLE COMPOUNDS

One final goal for the investigation of spirocyclobutene oxindoles was to explore the reactivity of these compounds and to determine if they could be further functionalized. The reactivity of alkylidene cyclobutene [2 + 2] adducts has yet been studied leading us to consider further reactions with these interesting compounds.

3.4.1 Hydrolysis of the Vinyl Acetate

One of the first transformations we investigated was hydrolysis of the vinyl acetate in spirooxindole **3.96**. By subjecting spirooxindole **3.96** to potassium carbonate in methanol and

water, ketone **3.119** was formed in quantitative yield as a single diastereomer. The key features in the ^{1}H NMR spectrum supporting the formation of **3.119** included the disappearance of the acetate CH_3 resonance at 1.79 ppm and the appearance of a new resonance integrating for 1H at 5.99 ppm, corresponding to the proton at C-6. Additionally, the IR spectrum showed a new stretch at 1710 cm^{-1} corresponding to the ketone. It was not initially known if protonation occurred at C-6 to yield **3.119** or at C-8 to produce **3.120**. In order to confirm the correct identity of the product, 2-dimentional NMR data including HMBC and HMQC was obtained. In the HMBC spectrum, a ^{3}J coupling between C-4 and the proton at C-6 was observed. This key coupling supported the identity of the product as spirooxindole **3.119**. Although we do not have data confirming the relative stereochemistry of **3.119**, it is predicted that the C-6 hydrogen will add from the less hindered face to provide the stereochemistry as shown in **3.119** (Scheme 3.44).

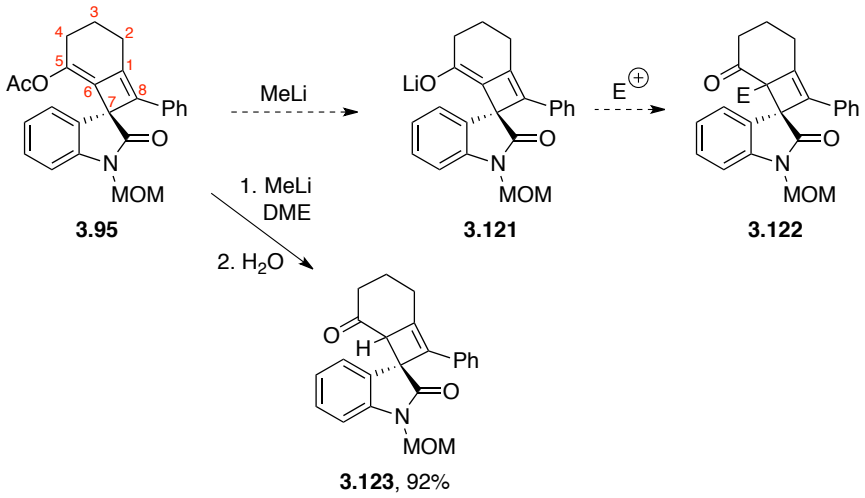


3.96 **3.119**, 100% **3.120**, 0%

Scheme 3.44 Hydrolysis of the Enol Acetate in Spirooxindole 3.96

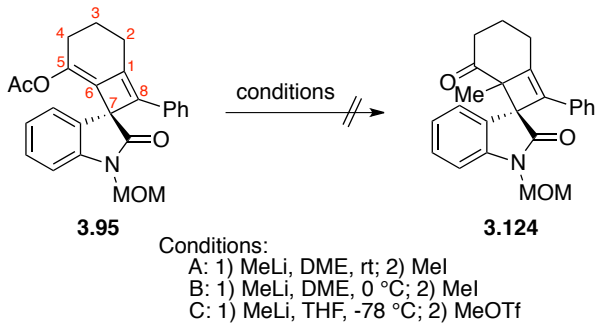
We were also interested in the deacylation of **3.95** using methyllithium. An advantage to this protocol is that if the enolate intermediate **3.121** is formed, then a variety of electrophiles could be introduced at C-6 to provide substituted products such as **3.122**. To examine this reaction, spirooxindole **3.95** was reacted with methyllithium in 1,2-dimethoxyethane (DME). After 20 min, water was added to quench the enolate. In this reaction, ketone **3.123** was formed in a 92% yield as a single diastereomer. The ^{1}H NMR spectrum of ketone **3.123** is very similar to

that of **3.119**, which was discovered previously. The key resonance in the ^{1}H NMR spectrum was for the new proton at C-6, which appeared as a singlet at 6.00 ppm (Scheme 3.45).



Scheme 3.45 Reacting Spirooxindole 3.95 with Methyllithium

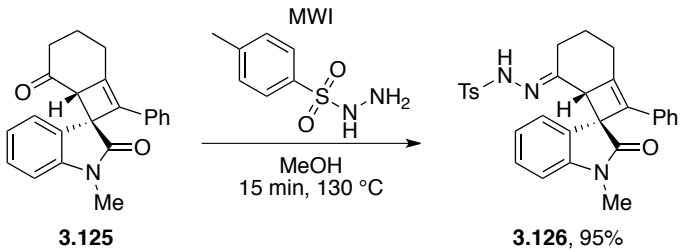
Based on the previous results using methyllithium and water, it was reasoned that by changing the electrophile from water to methyliodide, we could install a methyl group at C-6. As shown in Scheme 3.46, various conditions for the methylation were examined, but in all cases no desired methylation product **3.124** was obtained. In all cases, the isolated product from these reactions was the protonation product **3.123**. Even when water was rigorously excluded from the reaction using Schlenk techniques, only the protonation product was observed. One possibility for this result is that the enolate **3.121** is too sterically encumbered to allow electrophilic attack at the C-6 position (Scheme 4.46).



Scheme 3.46 Attempts to Install a Methyl Group at C-6 of Spirooxindole 3.95

3.4.2 Formation of Spirooxindole Hydrazone

We were interested in obtaining a crystal structure of one of the spirocyclobutane oxindole compounds prepared in our lab; however, all of the spirooxindoles prepared were oils and could not be crystalized. Upon preparation of ketone **3.125**, we envisioned conversion of the ketone to a hydrazone to obtain a crystalline compound. Microwave irradiation of ketone **3.125** with tosylhydrazine in methanol for 15 min at 130 °C provided the spirooxindole-hydrazone **3.126** in a 95% yield as a yellow powder. All attempts at crystallization were unsuccessful, but this reaction does demonstrate the utility of the ketone in the preparation of new, more highly functionalized compounds (Scheme 3.47).

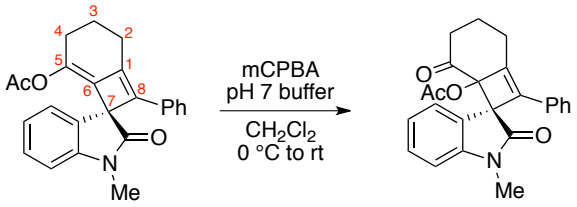


3.125 **3.126**, 95%

Scheme 3.47 Formation of Hydrazone 3.126

3.4.3 Subjecting the Spirocyclobutene Oxindoles to Epoxidation Conditions

Intrigued by the potential reactivity of the two alkenes present in the spirocyclobutene oxindole compounds, we chose to further functionalize these moieties. The first reaction examined was an epoxidation of spirooxindole **3.58**. Subjecting spirooxindole **3.58** to *m*-CPBA and sodium bicarbonate in dichloromethane led to complete decomposition of the reaction mixture. Based on this result, a more mild, buffered *m*-CPBA epoxidation was attempted. Reacting spirooxindole **3.58** with *m*-CPBA in pH 7 buffer and dichloromethane provided α-acetoxycarbonyl **3.127** in a 48% yield as a single diastereomer. It has previously been demonstrated that under epoxidation conditions, enolacetates can be converted to α-acetoxyketones via transfer of the acetate to the epoxide oxygen.[84] The key ^{1}H NMR resonance supporting the formation of spirocyclobutene oxindole **3.127** was the observed downfield shift of the acetate methyl from δ 1.77 to δ 2.03. In the ^{13}C NMR spectrum, a new ketone resonance was observed at δ 191.0. Also, to aid in structural confirmation of **3.127**, 2-dimentional HMQC and HMBC spectra were obtained (Scheme 3.48).

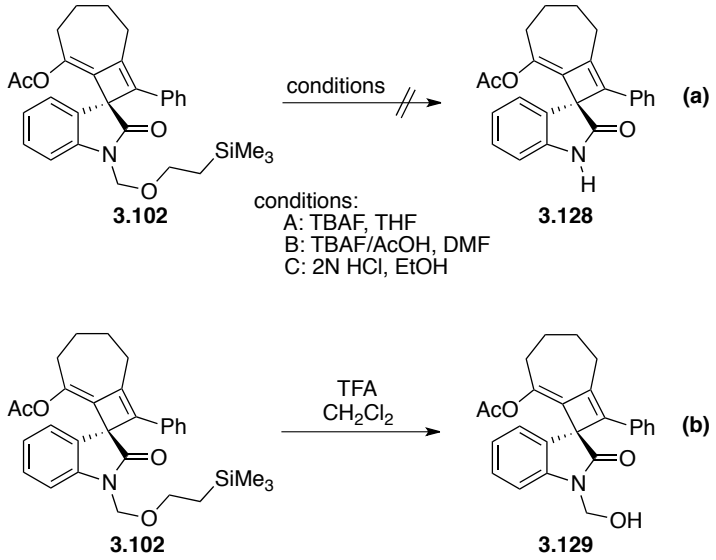


3.58 **3.127**, 48%

Scheme 3.48 Subjecting Spirooxindole 3.58 to a Buffered Epoxidation

3.4.4 Investigating Removal of the Oxindole Nitrogen Protecting Group

Finally, we investigated strategies to remove the amide protecting group because most biologically relevant oxindoles contain a free NH for the amide nitrogen. As shown in Scheme 3.49a, a number of unsuccessful conditions were employed. Reacting SEM protected oxindole **3.102** with TBAF affected no reaction at room temperature; upon heating, slow decomposition of the substrate occurred, with no observation of the desired product **3.128**. Additionally, reacting **3.102** with a 1:1 mixture of 2 N HCl and ethanol produced no reaction, possible due to poor solubility of spirooxindole **3.102** in the ethanol/$HCl_{(aq)}$ solvent. As shown in Scheme 3.49b, reacting spirooxindole **3.102** with trifluoroacetic acid (TFA) in dichloromethane resulted in a desilylation reaction to provide hemiaminal **3.129**. Although this reaction did not provide the fully deprotected oxindole, the hemiaminal **3.129** still provides a potentially biologically interesting compound. Conversion of hemiaminal **3.129** to the amide **3.128** was attempted by heating **3.129** in ammonium hydroxide and methanol, but no reaction occurred under these conditions (Scheme 3.49).



Scheme 3.49 Attempts to Deprotect the Oxindole Amide

3.4.5 Conclusions

In summary, there is still much work to be done on the functionalization reactions of the spirocyclobutene oxindole compounds. To date, only a few of many envisioned reactions have been performed. We have demonstrated deacylation of the spirooxindole products to provide the corresponding ketone. We have also shown that under epoxidation conditions, the spirooxindole enolacetates can be transformed to α-acetoxyketones. While deprotection of the amide has eluded us, we have demonstrated that that a partial deprotection of the SEM-oxindoles can be achieved using TFA to provide hemiaminal products. Additional reactions of the spirooxindole compounds including cyclopropanation, aziridination, dihydroxylation, and reductive amination of the ketones are of current interest in our laboratory.

3.5 CONCLUSIONS

This chapter began with the initial goal to expand the scope of the allen-yne [2 + 2] cycloaddition reaction to the synthesis of spirocyclobutene oxindoles. Preparation of 3-allenyloxindoles as a precursor to the spirooxindoles proved unsuccessful and led to the discovery of a new reaction: the thermal [3,3]-sigmatropic rearrangement/[2 + 2] cycloaddition of propargyl esters containing a tethered alkyne to provide carbocyclic spirooxindoles. The scope of this reaction was investigated and proved to be general with regard to group variations at the oxindole nitrogen, the ester, the alkyne terminus, and for the tether being lengthened. We reported the formation of both spirobicyclo[4.2.0]oxindoles and spirobicyclo[5.2.0]oxindoles in moderate yields. Next, chiral transfer from the propargylic acetate substrates to the spirooxindole products was explored. In substrates containing the enantiopure propargylic acetate, the reaction provided racemic spirooxindole products. When a bulky *t*-butyl group replaced the acetate, and the enantiopure 3-allenyloxindole was prepared, complete transfer of chiral information was observed in the [2 + 2] cycloaddition. We hypothesize that the bulkiness of the *t*-butyl group and oxindole restricts rotation at the intermediate diradical and thus prevents racemization. The final leg of this project focused on further functionalization of the spirooxindole compounds. The most notable transformations achieved were conversion of the enolacetate of the spirooxindole to the corresponding ketone and α-acetoxyketone.

In summary, we have developed a novel method for accessing highly functionalized carbocyclic spirooxindoles from relatively simple propargylic acetate substrates under purely thermal conditions. These compounds could potentially possess interesting biological properties. Work currently is underway to develop a library of spirooxindole compounds that can be submitted for biological evaluation.

4.0 EXPERIMENTAL SECTION

4.1 PREPARATION OF THE COMPOUNDS DESCRIBED IN CHAPTER 2

4.1.1 General Methods

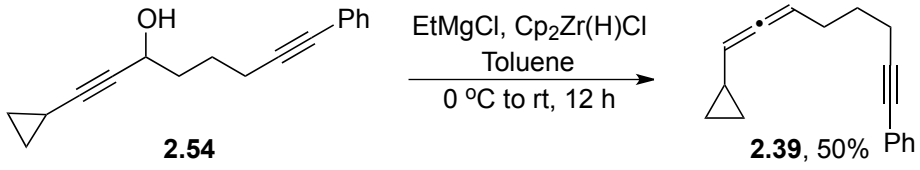
Unless otherwise noted, all reactions were performed in flame-dried glassware under an inert atmosphere of dry nitrogen. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, Acros Organics, and Advanced Chemtech and used as received. The reaction solvents tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were purified by passing through alumina using the Sol-Tek ST-002 solvent purification system. Triethylamine (NEt_3), toluene, and 1,2-dichlorobenzene were freshly distilled from CaH_2 prior to use. Benzene was freshly distilled from sodium/benzophenone prior to use. γ-Terpinene was purified by flash chromatography prior to use. Purification of the compounds by flash column chromatography was performed using silica gel (32-63 μm particle size, 60 Å pore size) purchased from Silicycle. TLC analyses were performed on EMD Chemicals Silica Gel 60 F_{254} glass plates (250 μm thickness). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz, 500 MHz, or 700 MHz spectrometers. Spectra were referenced to residual chloroform (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C), benzene (7.16 ppm, ^{1}H, 128.0 ppm, ^{13}C), 1,2-dichlorobenzene (6.93 ppm, ^{1}H, 127.19 ppm, ^{13}C)

or *N,N*-dimethylformamide (8.38 ppm, ^{1}H). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), and m (multiplet). Coupling constants, *J*, are reported in hertz. All NMR spectra were obtained at room temperature unless otherwise specified. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectroscopy was performed on a Micromass Autospec high resolution mass spectrometer. Melting points were uncorrected and determined on a Mel-Temp instrument. All microwave-mediated reactions were carried out using a Biotage Initiator™ Exp microwave synthesizer. The microwave parameters were set to variable power, constant temperature, with the fixed hold time set to on. The microwave reactions were carried out in 0.2-0.5 mL, 0.5-2 mL, or 2-5 mL Biotage microwave vials.

4.1.2 Literature Preparations

Aldehyde **2.53** was prepared via a Swern oxidation of the corresponding alcohol as reported by Liu.[85] The protocol for formation of allenes from propargyl alcohols was first reported by Ready and Pu in 2007.[39] Preparation of cyclopropyl aldehydes **2.59** and **2.65** followed the procedure reported by Tadic-Biadatti and Newcomb.[33b] Diyne **2.60** was prepared as reported by Yamamoto.[40] Allene **2.72** was prepared previously in our group.[7]

4.1.3 Detailed Experimental Protocols



2.54 **2.39**, 50%

1-(8-Cyclopropylocta-6,7-dien-1-ynyl)benzene (2.39). A flame-dried 25 mL round-bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **2.54** (0.400 g, 1.68 mmol) and toluene (8.4 mL). The solution was cooled to 0 °C at which time ethyl magnesium chloride (0.84 mL of a 2.0 M diethyl ether solution, 1.68 mmol) was added dropwise. The reaction was allowed to stir at 0 °C for 10 min and was then warmed to rt and stirred an additional 10 min. Zirconocene chloride hydride (0.433 g, 1.68 mmol) was then added in one portion. The reaction was wrapped in aluminum foil and left to stir overnight. The reaction mixture was filtered through a plug of Celite, which was subsequently washed with ether (15 mL). To the filtrate was added saturated sodium bicarbonate solution (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to provide a yellow oil. The residue was purified by silica gel flash chromatography eluting with a gradient of 100% hexanes to 2% ethyl acetate/hexanes. The fractions containing the desired product were concentrated under reduced pressure to provide 0.211 g of allene-yne **2.39** as a colorless oil in 57% yield.

Data for **2.39**: (JMO3-33)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.42 – 7.37 (m, 2H), 7.30 – 7.25 (m, 3H), 5.21 (ddt, *J* = 1.2, 6.6, 6.6 Hz, 1H), 5.00 (ddt, *J* = 7.2, 6.6, 2.7 Hz, 1H), 2.46 (t, *J* = 7.2 Hz, 2H), 2.16 (ddt, *J* = 2.7, 7.2, 7.2 Hz, 2H), 1.72 (p, *J* = 7.2 Hz, 2H), 1.30 – 1.18 (m, 1H), 0.72 – 0.66 (m, 2H), 0.37 – 0.33 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 203.4, 131.5 (2C), 128.2 (2C), 127.5, 124.0, 95.6, 91.9, 89.9, 80.8, 28.2, 28.1, 18.8, 9.6, 6.8, 6.6

IR (thin film)

3003, 2938, 2230, 1959 cm^{-1}

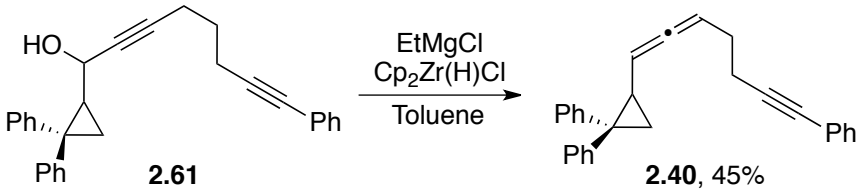
MS EI+

m/z (%) 235 (7), 222 (45), 221 (70), 194 (57), 193 (45), 179 (50), 178 (40), 165 (40), 128 (55), 119 (89), 117 (92), 115 (88), 91 (87), 79 (43), 77 (53), 69 (100)

HRMS EI-HRMS: $C_{17}H_{18}$

Calculated: 222.1409 Found: 222.1400

TLC R_f = 0.75 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-(1-Phenyl-2-(7-phenylhepta-1,2-dien-6-ynyl)cyclopropyl)benzene (2.40). A flame-dried 5 mL round bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **2.61** (292 mg, 0.75 mmol) plus toluene (3.7 mL). The solution was cooled to 0 °C at which time ethyl magnesium chloride (0.37 mL of a 2.0 M diethyl ether solution, 0.75 mmol) was added dropwise via syringe. The reaction was maintained at 0 °C for 10 min then warmed to rt and stirred for an additional 10 min. Zirconocene chloride hydride (193 mg, 0.75 mmol) was then added in one portion. The reaction flask was wrapped in aluminum foil and left to stir overnight. The reaction was quenched by adding saturated aqueous sodium bicarbonate (2 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 2 mL). The combined

organic layers were washed with brine (3 mL), dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography eluting with a gradient of 100% hexanes to 2% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide 125 mg of allene **2.40** as a colorless oil in 45% yield.

Data for **2.40**: (JMO3-52)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.42-7.11 (m, 15H), 5.18 (ddt, *J* = 6.6, 6.6, 1.2 Hz, 1H), 4.81 (ddt, *J* = 7.7, 6.1, 3.0 Hz, 1H), 2.34 (t, *J* = 7.2 Hz, 2H), 2.16 (dddd, *J* = 8.7, 7.6, 6.3, 1.3 Hz, 1H), 1.96-1.74 (m, 2H), 1.58-1.46 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 204.6, 146.5, 141.2, 131.5 (2C), 131.3 (2C), 128.2 (2C), 128.2 (2C), 128.2 (2C), 127.5, 127.2 (2C), 126.5, 125.7, 124.0, 92.1, 91.7, 90.0, 80.8, 37.4, 28.1, 27.9, 26.3, 21.2, 18.8

IR (thin film)

3077, 3057, 3024, 2931, 1958 cm^{-1}

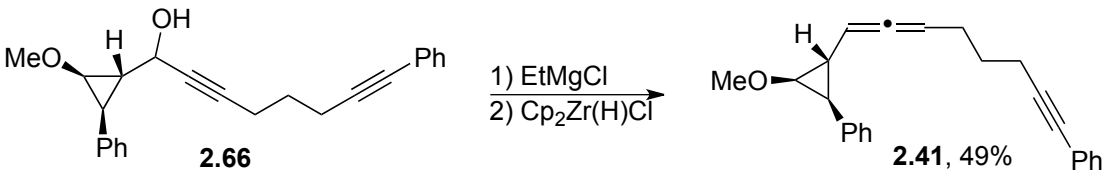
MS EI+

m/z (%) 374 (28), 283 (35), 194 (35), 178 (29), 167 (37), 165 (57), 128 (35), 115 (100), 91 (74), 77 (25)

HRMS EI-HRMS: $C_{29}H_{26}$

Calculated: 374.2035 Found: 374.2025

TLC R_f = 0.42 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-(2-Methoxy-3-(8-phenylocta-1,2-dien-7-ynyl)cyclopropyl)benzene (2.41). A flame-dried 25 mL round-bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **2.66** (0.620 g, 1.80 mmol) and toluene (9 mL). The solution was cooled to 0 °C at which time ethyl magnesium chloride (0.90 mL of a 2.0 M diethyl ether solution, 1.80 mmol) was added dropwise. The reaction was allowed to stir at 0 °C for 10 min and was then warmed to rt and stirred an additional 10 min. Zirconocene chloride hydride (0.511 g, 1.98 mmol) was then added in one portion. The reaction flask was wrapped in aluminum foil and the reaction was left to stir overnight. The reaction mixture was filtered through a plug of celite which was subsequently washed with ether (15 mL). To the filtrate was added saturated sodium bicarbonate solution (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous sodium sulfate, filtered, and concentrated to provide a yellow oil. The residue was purified by silica gel flash chromatography eluting with 4% ethyl acetate/hexanes. The fractions containing the desired product were concentrated under reduced pressure to provide 0.288 g of allene-yne **2.41** as a lightly colored oil in 49% yield.

Data for **2.41**: (JMO3-163)

^{1}H NMR (300 MHz, C_6D_6)

δ 7.47 – 7.44 (m, 2H, major and minor), 7.29 – 7.26 (m, 2H, major and minor), 7.18 – 7.13 (m, 3H, major and minor), 7.09 – 7.02 (m, 1H, major and minor), 6.98 – 6.93 (m, 2H, major and minor), 5.23 – 5.08 (m, 2H, major and minor), 3.26 (dd, *J* = 3.3, 6.6 Hz, 1H, major), 3.25 (dd, *J* = 3.3, 6.6 Hz, 1H, minor), 2.93 (s, 3H, minor), 2.92 (s, 3H, major) 2.24 (t, *J* = 6.9 Hz, 2H, major and minor), 2.06 – 1.95

(m, 3H, major and minor), 1.91 – 1.85 (m, 1H, major and minor), 1.59 – 1.48 (m, 2H, major and minor)

^{13}C NMR (75 MHz, C_6D_6)

δ 203.8 (minor), 203.7 (major), 137.41 (minor), 137.37 (major), 131.6 (2C, major and minor), 128.2 (2C, major and minor), 128.1 (major and minor), 127.9 (2C, major and minor), 127.5 (major and minor), 125.7 (2C, major and minor), 124.4 (major and minor), 92.8 (major), 92.7 (minor), 92.4 (minor), 92.3 (major), 89.80 (minor), 89.77 (major), 81.52 (major), 81.49 (minor), 67.3 (major), 67.1 (minor), 57.5 (major and minor), 32.2 (minor), 32.0 (major), 28.0 (major and minor), 27.93 (major), 27.88 (minor), 25.0 (minor), 24.8 (major), 18.7 (major and minor)

IR (thin film)

3028, 2932, 1958, 1727, 1601 cm^{-1}

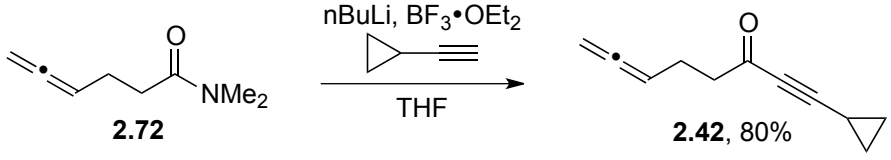
MS EI+

m/z (%) 363 (40), 351 (58), 342 (62), 335 (61), 330 (52), 294 (61), 229 (100), 227 (70), 217 (43), 145 (51)

HRMS TOF MS ES+: $C_{24}H_{24}ONa$

Calculated: 351.1725 Found: 351.1709

TLC R_f = 0.57 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



2.72 **2.42**, 80%

1-Cyclopropylocta-6,7-dien-1-yn-3-one (2.42). A flame-dried 50 mL round-bottomed flask under a nitrogen atmosphere was charged with cyclopropylacetylene (0.342 g, 5.17 mmol) and tetrahydrofuran (11.5 mL) and cooled to -78 °C. To this solution was added *n*-butyllithium (2.87

mL of a 1.6 M hexanes solution, 4.59 mmol) dropwise over a period of 10 min. The solution was maintained at -78 °C for 5 min at which time borontrifluoride diethyletherate (0.61 mL, 4.88 mmol) was added via syringe. The reaction was maintained at -78 °C for 15 min at which time amide **2.72** (400 mg, 2.87 mmol) was added as a solution in tetrahydrofuran (11.5 mL) dropwise via syringe. The mixture was stirred at -78 °C for 2 h. Additional borontrifluoride diethyletherate (0.61 mL, 4.88 mmol) was added followed by acetic acid (0.28 mL, 4.88 mmol). The reaction was immediately allowed to warm to -20 °C at which time it was quenched by the addition of saturated aqueous ammonium chloride solution (10 mL). The reaction mixture was then poured into a separatory funnel containing ether (10 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with 20% ether/pentane to afford 0.460 g of ynone **2.42** in an 80% yield as a clear oil.

Data for **2.42**: (JMO2-177)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 5.15 (dt, J = 13.1, 6.5 Hz, 1H), 4.72 (dt, J = 6.6, 3.6 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 2.37 – 2.28 (m, 2H), 1.442 – 1.35 (m, 1H), 1.01 – 0.88 (m, 4H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 208.3, 186.8, 98.8, 88.5, 76.5, 76.0, 43.9, 22.3, 9.6 (2C), -0.41

IR (thin film)

3014, 2205, 1956, 1669 cm^{-1}

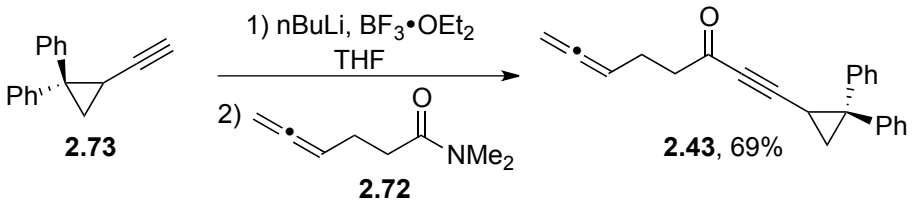
MS EI+

m/z (%) 161 (56), 160 (70), 145 (95), 141 (68), 133 (82), 129 (70), 116 (91), 108 (82), 107 (94), 105 (100), 94 (89), 92 (75), 90 (77), 67 (89), 64 (84), 62 (98)

HRMS EI-HRMS: $C_{11}H_{12}O$

Calculated: 160.0888 Found: 160.0883

TLC R_f = 0.30 (10% EtOAc/hexanes) [silica gel, *p*-anisaldehyde stain]



1-(2,2-Diphenylcyclopropyl)octa-6,7-dien-1-yn-3-one (2.43). A flame-dried 25 mL two-necked round-bottomed flask equipped with a nitrogen inlet and a septa was charged with alkyne **2.73** (321 mg, 1.47 mmol) and tetrahydrofuran (3.3 mL). The solution was cooled to -78 °C and *n*-butyllithium (0.82 mL of a 1.6 M hexanes solution, 1.31 mmol) was added dropwise via syringe. The reaction was held at -78 °C for 20 min at which time borontrifluoride diethyl etherate (0.174 mL, 1.39 mmol) was added via syringe. The reaction was held at -78 °C for 15 min at which time amide **2.72** was added as a solution in tetrahydrofuran (3.3 mL) dropwise via syringe. The reaction was stirred at -78 °C for 2 h at which time complete consumption of the starting material was observed by TLC. Additional borontrifluoride diethyl etherate (0.174 mL, 1.39 mmol) was added followed by acetic acid (79.6 μL, 1.39 mmol). The reaction was allowed to warm to *ca*. -20 °C at which time saturated aqueous ammonium chloride (6 mL) was added and the reaction was allowed to warm to rt. The layers were separated and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to provide a dark yellow oil. The residue was purified by silica gel flash chromatography eluting with a gradient of 4% - 7% ethyl

acetate/hexanes. The fractions containing the desired product were concentrated under reduced pressure to afford 177 mg of allene-ynone **2.43** as light yellow oil in 69% yield.

Data for **2.43**: (JMO4-16)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.42 – 7.20 (m, 10H), 4.99 (p, *J* = 6.3 Hz, 1H), 4.69 (t, *J* = 3.6 Hz, 1H), 4.67 (t, *J* = 3.6 Hz, 1H), 2.33 (dd, *J* = 8.7, 6.4 Hz, 1H), 2.26 (t, *J* = 7.8 Hz, 2H), 2.03 – 1.94 (m, 2H), 1.91 (dd, *J* = 4.8, 5.4 Hz, 1H), 1.80 (dd, *J* = 4.8, 9.0 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 208.2, 186.9, 143.6, 140.0, 129.9 (2C), 128.6 (2C), 128.3 (2C), 127.9 (2C), 127.2, 126.9, 95.4, 88.5, 81.5, 76.1, 43.8, 40.0, 23.9, 22.1, 15.6

IR (thin film)

3058, 3026, 2918, 2201, 1956, 1668, 1600 cm^{-1}

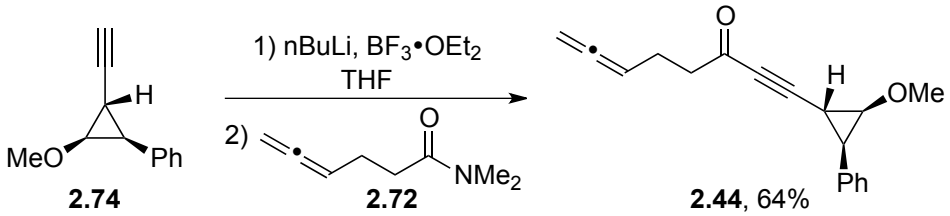
MS EI+

m/z (%) 312 (6), 311 (11), 221 (52), 223 (48), 215 (88), 202 (62), 180 (45), 179 (88), 178 (79), 165 (100), 115 (62), 91 (63)

HRMS EI-HRMS: $C_{23}H_{20}ONa$

Calculated 335.1412; Found 335.1404

TLC R_f = 0.51 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



2.74 **2.72** **2.44**, 64%

1-(2-Methoxy-3-phenylcyclopropyl)octa-6,7-dien-1-yn-3-one (2.44). A flame-dried 5 mL pear-shaped flask under a nitrogen atmosphere was charged with alkyne **2.74** (63 mg, 0.366

mmol) and tetrahydrofuran (0.82 mL). The solution was cooled to -78 °C and *n*-butyllithium (0.20 mL of a 1.6 M hexanes solution, 0.325 mmol) was added dropwise via syringe. The reaction was held at -78 °C for 20 min at which time borontrifluoride diethyl etherate (43.5 µL, 0.346 mmol) was added via syringe. The reaction was held at -78 °C for 15 min at which time amide **2.72** (28.3 mg, 0.203 mmol) was added as a solution in tetrahydrofuran (0.82 mL) dropwise via syringe. The reaction was stirred at -78 °C for 2 h at which time complete consumption of the starting material was observed by TLC. Additional borontrifluoride diethyl etherate (43.5 µL, 0.346 mmol) was added followed by acetic acid (19.8 µL, 0.346 mmol). The reaction was allowed to warm to -20 °C at which time saturated aqueous ammonium chloride solution (3 mL) was added and the reaction was allowed to warm to rt. The layers were separated and the aqueous layer was extracted with ether (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated to give a light yellow oil. The oil was adsorbed onto silica gel and applied to a silica gel column using the typical dry loading technique. The column was eluted with 7% ethyl acetate/ hexanes. The fractions containing the desired product were concentrated under reduced pressure to afford 34.7 mg of ynone **2.44** as clear oil in 64% yield.

Data for **2.44**: (JMO4-26)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.36 – 7.24 (m, 5H), 5.19 (p, *J* = 6.3 Hz, 1H), 4.77 (t, *J* = 3.3 Hz, 1H), 4.74 (t, *J* = 3.3 Hz, 1H), 3.79 (dd, *J* = 3.0, 6.9 Hz, 1H), 3.36 (s, 3H), 2.69 (t, *J* = 7.2 Hz, 2H), 2.57 (t, *J* = 6.9 Hz, 1H), 2.41 – 2.32 (m, 2H), 1.96 (dd, *J* = 3.3, 6.6 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 208.4, 186.7, 134.2, 128.2 (3C), 126.9, 94.3, 88.5, 78.5, 76.2, 67.0, 58.7, 44.0, 34.2, 22.3, 15.2

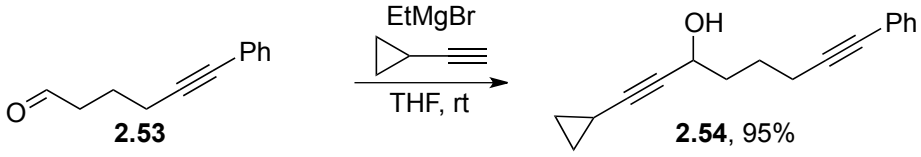
IR (thin film)

2933, 2199, 1955, 1668 cm^{-1}

HRMS EI-HRMS: $C_{18}H_{18}O_2$

Calculated: 266.1307 Found: 266.1299

TLC R_f = 0.46 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-Cyclopropyl-8-phenylocta-1,7-diyn-3-ol (2.54). A flame dried, 25 mL single necked round-bottomed flask under a nitrogen atmosphere was charged with cyclopropyl acetylene (0.173 g, 2.62 mmol) and tetrahydrofuran (2.6 mL). To this solution was added ethyl magnesium bromide (0.87 mL of a 3.0 M diethyl ether solution, 2.62 mmol) dropwise over 5 min. The reaction was allowed to stir at room temperature for 1 h at which time aldehyde **2.53** (0.500 g, 2.91 mmol) was added dropwise as a solution in tetrahydrofuran (8.3 mL). The reaction was allowed to stir for 2 h at room temperature at which time all starting material had been consumed based on TLC. The reaction was quenched by adding saturated aqueous ammonium chloride solution (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (15 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with 20% ethyl acetate/hexanes to provide 0.655 g of the title compound **2.54** as a colorless oil in a 95% yield.

Data for **2.54**: (JMO3-29)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.45 – 7.39 (m, 2H), 7.30 – 7.27 (m, 3H), 4.41 (dq, *J* = 1.2, 5.7 Hz, 1H), 2.47 (t, *J* = 6.9 Hz, 2H), 1.91 – 1.73 (m, 5H), 1.30 – 1.24 (m, 1H), 0.815 – 0.734 (m, 2H), 0.717 – 0.665 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 131.5 (2C), 128.1 (2C), 127.5, 123.8, 89.7, 88.8, 81.0, 76.2, 62.2, 37.2, 24.4, 19.1, 8.2, -0.7

IR (thin film)

3356, 3013, 2948, 2865, 2240 cm^{-1}

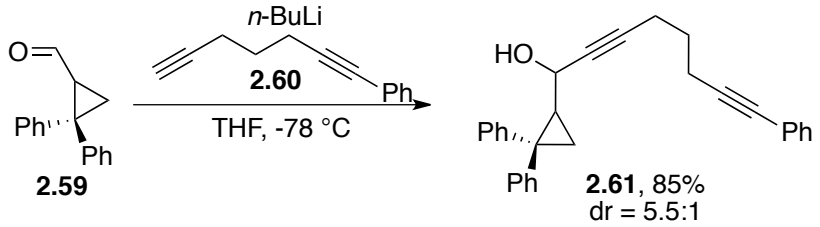
MS EI+

m/z (%) 263 (12), 261 (53), 259 (60), 229 (100), 227 (70), 217 (50), 216 (38), 215 (25), 173 (23), 159 (10), 147 (15), 145 (20)

HRMS TOF MS ES+: $C_{17}H_{18}ONa$

Calculated 261.1255 Found: 261.1262

TLC R_f = 0.24 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



8-Phenyl-1-(2,2-diphenylcyclopropyl)octa-2,7-diyn-1-ol (2.61). A flame-dried round-bottomed flask under a nitrogen atmosphere was charged with diyne **2.60** (272 mg, 1.62 mmol) and tetrahydrofuran (8 mL) and cooled to -78 °C. *n*-Butyllithium (0.93 mL of a 1.6 M hexanes

solution, 1.48 mmol) was added dropwise via syringe and the reaction was maintained at -78 °C for 1 h. To the acetylide solution was added aldehyde **2.59** (300 mg, 1.35 mmol) as a solution in tetrahydrofuran (2.7 mL). The reaction was maintained at -78 °C for 40 min, then warmed to 0 °C at which time all starting material had been consumed based on TLC. The reaction was quenched by adding saturated aqueous ammonium chloride solution (10 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude material was purified by silica gel flash chromatography eluting with a gradient of 15% - 25% ethyl acetate/hexanes to provide propargyl alcohol **2.61** as a 5.5:1 mixture of separable diastereomers in an 85% combined yield (major, 378 mg, 72%; minor, 68 mg, 13%).

Data for **2.61**: (JMO3-58)

Major Diastereomer

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.47 – 7.43 (m, 2H), 7.40 – 7.37 (m, 2H), 7.33 – 7.21 (m, 10H), 7.20 – 7.12 (m, 1H), 3.63 (ddt, J = 9.0, 4.8, 1.8 Hz, 1H), 2.50 (t, J = 6.9 Hz, 2H), 2.39 (dt, J = 1.8, 6.9 Hz, 2H), 2.09 (ddd, J = 5.7, 9.0, 9.0 Hz, 1H), 1.79 (p, 6.9 Hz, 2H), 1.77 (d, J = 4.8 Hz, 1H), 1.45 (t, J = 5.7 Hz, 1H), 1.32 (dd, J = 9.0, 5.4 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 145.9, 140.6, 131.5 (2C), 130.3 (2C), 128.5 (2C), 128.3 (2C), 128.2 (2C), 128.0 (2C), 127.6, 126.8, 126.1, 123.8, 89.1, 83.8, 81.3, 81.2, 63.4, 37.0, 32.8, 27.8, 18.5, 18.0, 17.1

TLC R_f = 0.30 (30% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

Minor Diastereomer

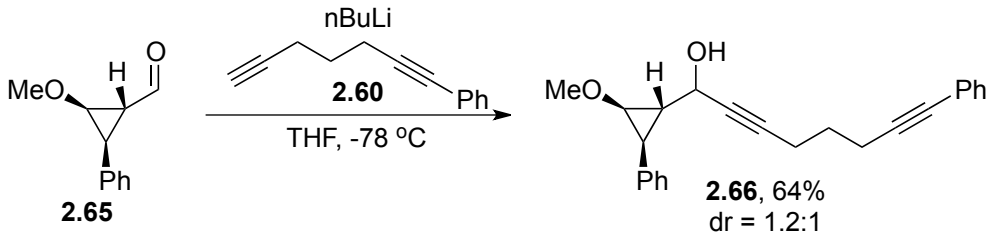
^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.53 – 7.50 (m, 2H), 7.46 – 7.43 (m, 2H), 7.36 – 7.24 (m, 5H), 7.22 – 7.15 (m, 1H), 3.53 (dt, *J* = 9.6, 1.5 Hz, 1H), 2.62 (t, *J* = 6.9 Hz, 2H), 2.51 (tt, *J* = 6.9, 1.5 Hz, 2H), 2.17 (ddd, *J* = 9.3, 6.0, 6.0 Hz, 1H), 1.90 (p, *J* = 6.9 Hz, 2H), 1.60 (t, *J* = 5.4 Hz, 1H), 1.38 (dd, *J* = 5.1, 8.7 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 146.0, 140.7, 131.5 (2C), 130.2 (2C), 128.3 (2C), 128.3 (2C), 128.2 (2C), 128.0 (2C), 127.6, 126.8, 126.1, 123.7, 88.9, 84.8, 81.4, 81.3, 64.2, 36.0, 32.7, 27.6, 18.5, 18.3, 17.9

TLC R_f = 0.17 (30% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-(2-Methoxy-3-phenylcyclopropyl)-8-phenylocta-2,7-diyn-1-ol (2.66). A 50 mL flame-dried round-bottomed flask under a nitrogen atmosphere was charged with diyne **2.60** (0.573 g, 3.41 mmol) and tetrahydrofuran (17 mL). The solution was cooled to -78 °C at which time *n*-butyllithium (1.95 mL or a 1.6 M hexanes solution, 3.13 mmol) was added dropwise by syringe. The solution was stirred at -78 °C for 30 min at which time aldehyde **2.65** (0.500 g, 2.84 mmol) was added dropwise as a solution in tetrahydrofuran (5.7 mL). The reaction was maintained at -78 °C for 1.5 h at which time all starting material had been consumed based on TLC. Saturated aqueous ammonium chloride solution (15 mL) was added and the reaction was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (20 mL), dried over

anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography eluting with a gradient of 25% to 30% ethyl acetate/hexanes to provide 0.627 g of propargyl alcohol **2.66** as a colorless oil in 64% yield as a 1.2:1 ratio of diastereomers (ration determined by integration of the methoxy protons.

Data for **2.66**: (JMO4-94)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.40 – 7.37 (m, 2H, major and minor), 7.28 – 7.24 (m, 7H, major and minor), 7.20 – 7.16 (m, 1H, major and minor), 4.55 (br s, 1H, minor), 4.71 (br s, 1H, major), 3.55 (dd, *J* = 3.0, 7.0 Hz, 1H, major), 3.48 (dd, *J* = 3.5, 7.0 Hz, 1H, minor), 3.18 (s, 3H, major), 3.16 (s, 3H, minor), 2.53 (t, *J* = 6.5 Hz, 2H) 2.51 (t, *J* = 6.5 Hz, 1H), 2.41 (m, 2H, major and minor), 2.24 (t, *J* = 7.0 Hz, 1H, minor), 2.17 (t, *J* = 7.0 Hz, major), 1.97 (d, *J* = 5.0 Hz, 1H, minor), 1.89 – 1.84 (m, 2H major, 1H minor), 1.83 – 1.78 (m, 2H, major and minor)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 136.6 (major and minor), 131.6 (2C, major and minor), 128.2 (2C, major and minor), 128.1 (2C, major and minor), 128.0 (2C, major and minor), 127.7 (major and minor), 125.9 (major and minor), 123.7 (major and minor), 88.8 (major and minor), 85.7 (major and minor), 81.4 (major and minor), 79.4 (major and minor), 63.4, 62.8, 62.6 (major and minor), 58.3 (major and minor), 31.7, 31.6, 28.0, 27.7 (major and minor), 26.5, 18.6 (major and minor), 17.9 (major and minor)

IR (thin film)

3397, 3027, 2935, 2828, 2228, 1601cm^{-1}

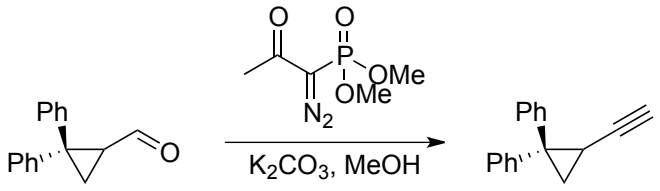
MS EI+

m/z (%) 237 (52), 148 (79), 129 (57), 128 (64), 115 (100), 105 (87), 103 (50), 91 (81), 77 (79)

HRMS EI-HRMS: $C_{24}H_{24}O_2$

Calculated: 344.1776 Found: 344.1770

TLC R_f = 0.14 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



2.59 **2.73**, 70%

1-(2-Ethynyl-1-phenylcyclopropyl)benzene (2.73). A flame-dried 50 mL two-necked round-bottomed flask equipped with a nitrogen inlet and septa was charged with aldehyde **2.59** (0.226 g, 1.02 mmol) and methanol (12 mL). To this solution was added potassium carbonate (0.281 g, 2.03 mmol) followed by the Bestmann-Ohira reagent (0.234 g, 1.22 mmol) in methanol (3.0 mL). The reaction was stirred for 4 h at which time complete consumption of starting material was observed by TLC. The reaction mixture was diluted with ether (50 mL). This mixture was then transferred to a separatory funnel containing 5% aqueous sodium bicarbonate (25 mL). The layers were separated and the organic layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure to produce 0.142 g of the title compound **2.73** as a clear oil in 64% yield. No further purification was necessary.

Data for **2.73**: (JMO4-14)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.45 – 7.14 (m, 10H), 2.22 – 2.16 (ddd, *J* = 2.4, 6.0, 9.0 Hz, 1H), 1.87 (d, *J* = 2.1 Hz, 1H), 1.71 (dd, *J* = 4.8, 6.0 Hz, 1H), 1.64 (dd, *J* = 4.5, 9.0 Hz, 1H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 144.7, 140.6, 130.1(2C), 128.4(2C), 128.1(2C), 128.0(2C), 126.8, 126.5, 83.9, 69.6, 37.6, 22.8, 15.5

IR (thin film)

3291, 3082, 3058, 3026, 2919, 1226, 1598, 1495 cm^{-1}

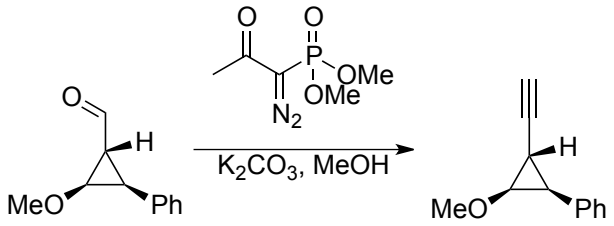
MS EI+

m/z (%) 219 (20), 218 (89), 217 (66), 215 (46), 202 (53), 165 (57), 149 (67), 140 (43), 115 (46), 71 (65), 69 (45), 57 (100), 65 (65)

HRMS EI-HRMS: $C_{17}H_{14}$

Calculated 218.1096; Found 218.1088

TLC R_f = 0.71 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



2.65 **2.74**, 42%

1-(2-Ethynyl-3-methoxycyclopropyl)benzene (2.74). A flame-dried 50 mL two-necked round-bottomed flask equipped with a nitrogen inlet and septa was charged with aldehyde **2.65** (0.260 g, 1.48 mmol) and methanol (15 mL). To this solution was added potassium carbonate (0.408 g, 2.95 mmol) followed by the Bestmann-Ohira reagent (0.341 g, 1.78 mmol) in methanol (7.0 mL). The reaction was stirred for 4 h at which time complete consumption of starting material was observed by TLC. The reaction mixture was diluted with ether (50 mL). This mixture was then transferred to a separatory funnel containing 5% aqueous sodium bicarbonate (30 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 25 mL). The

combined organic layers were washed with brine (25 mL), dried over magnesium sulfate, filtered, and concentrated under reduced pressure to provide a dark yellow oil. The residue was purified by silica gel flash chromatography eluting with 6% ethyl acetate/hexanes to afford 141 mg of the title compound **2.74** as a clear oil in 55% yield.

Data for **2.74**: (JMO4-96)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.36 – 7.24 (m, 5H), 3.69 (dd, *J* = 3, 7.0 Hz, 1H), 3.34 (s, 3H), 2.40 (t, *J* = 6.5 Hz, 1H), 2.00 (d, *J* = 2.0 Hz, 1H), 1.88 (ddd, *J* = 2.1, 3, 6.6 Hz, 1H)

^{13}C NMR (125 MHz, $CDCl_3$)

δ 135.1, 128.13 (2C), 128.08 (2C), 126.5, 83.9, 66.2, 66.0, 58.5, 32.8, 14.8

IR (thin film)

3292, 3029, 2990, 2935, 2828, 2115, 1603 cm^{-1}

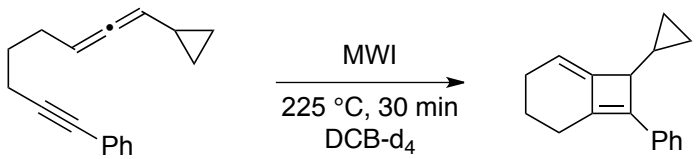
MS EI+

m/z (%) 173 (52), 172 (100), 171 (86), 157 (65), 142 (64), 141 (90), 140 (67), 129 (90), 128 (92), 127 (76), 115 (78), 105 (68), 91 (72), 84 (62), 77 (68), 63 (61)

HRMS EI-HRMS: $C_{12}H_{12}O$

Calculated: 172.0888 Found: 172.0887

TLC R_f = 0.56 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



2.39 **2.75**, 83%

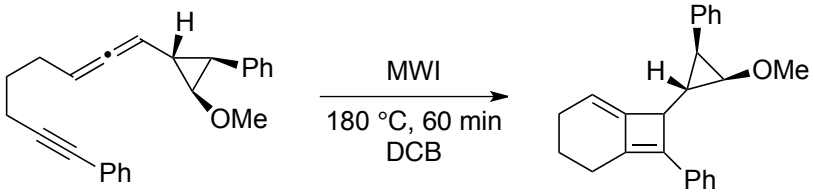
8-Cyclopropyl-7-phenylbicyclo[4.2.0]octa-1,6-diene (2.75). An NMR tube was charged with allene-yne **2.39** (11.3 mg, 0.051 mmol) and deuterated *o*-dichlorobenzene (0.5 mL). 1,4-dimethoxybenzene (1.4 mg, 0.010 mmol) was added as an internal standard and a ^{1}H NMR (16 scans, 10 s delay time) was obtained. The solution was then transferred to a 0.2 - 0.5 mL Biotage™ microwave vial that was capped with a Reseal™ septum. The solution was irradiated in the microwave for 30 min at 225 °C. A ^{1}H NMR (16 scans, 10 s delay time) of the reaction mixture showed complete conversion of allene-yne **2.39** to alkylidene cyclobutene **2.75**. Based on integration of the cyclopropane protons in the starting material and product in relation to the internal standard, the yield was calculated to be 83%.

Data for **2.75**: (JMO3-28)

^{1}H NMR (300 MHz, *o*-dichlorobenzene-d_4)

δ 7.37 (d, J = 7.2 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 7.12 (t, J = 7.5 Hz, 1H), 5.26 (t, J = 3.9 Hz, 1H), 3.39 – 3.37 (m, 1H), 2.49 – 2.28 (m, 2H), 2.13 – 2.07 (m, 2H), 1.72 (p, J = 6.3 Hz, 2H), 1.09 – 0.98 (m, 1H), 0.59 – 0.53 (m, 1H), 0.38 – 0.30 (m, 3H)

TLC R_f = 0.71 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



2.41 **2.77**, 85%

8-(2-Methoxy-3-phenylcyclopropyl)-7-phenylbicyclo[4.2.0]octa-1,6-diene (2.77). An NMR tube was charged with allene-yne **2.41** (9.0 mg, 0.027 mmol) and deuterated *o*-dichlorobenzene (0.4 mL). Additionally, *p*-dimethoxybenzene was added as an internal standard and a ^{1}H NMR

(16 scans, 10 s delay time) was obtained. The solution was transferred to a 0.2 – 0.5 mL Biotage™ microwave vial and the vial was capped with a Reseal™ septum. The solution was irradiated in the microwave at 180 °C for 2h at which time all starting material had been consumed and one new product had formed, based on TLC analysis. The reaction mixture was transferred to an NMR tube and a ^{1}H NMR (16 scans, 10 s delay time) was obtained. The NMR showed complete conversion of allene-yne **2.41** to alkylidene cyclobutene **2.77**. Based on integration of the methoxy protons of the starting material and product in relation to the integration of the internal standard, the yield was calculated to be 85%.

Data for **2.77**: (JMO3-177)

^{1}H NMR (300 MHz, *o*-dichlorobenzene-d_4)

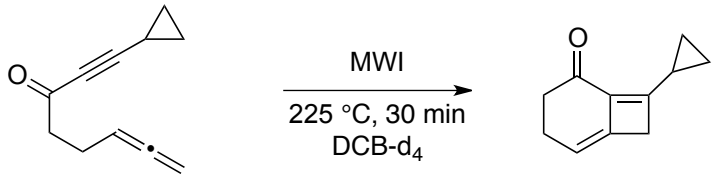
δ 7.44 – 7.00 (m, 10H, major and minor), 5.38 (br s, 1H, minor), 5.27 (br s, 1H, major), 3.46 – 3.41 (m, 2H, major and minor), 3.07 (s, 3H, major), 3.01 (s, 3H, minor) 2.50 – 2.31 (m, 2H major and minor, 1H major or minor), 2.16 – 2.13 (m, 1H, major and minor), 2.09 – 1.98 (m, 2H, major and minor, 1H major or minor), 1.77 – 1.69 (m, 3H, major and minor)

^{13}C NMR (75 MHz, *o*-dichlorobenzene-d_4)

δ 153.9 (major and minor), 142.2 (major and minor), 141.3 (minor), 141.2 (major), 140.8 (minor), 140.5 (major), 138.3 (minor), 138.2 (major), 135.2 (major), 135.1 (minor), 128.5 (2C, major and minor), 128.3 (2C, major), 128.2 (2C, minor), 127.9 (2C, minor), 127.8 (2C, major), 126.4 (2C, major and minor), 125.5 (minor), 125.4 (major), 110.0 (minor), 109.9 (major), 66.0 (major), 63.7 (minor), 57.8 (major), 57.7 (minor), 50.0 (minor), 49.9 (major), 30.9, 28.2, 27.8

(major), 27.5 (minor), 24.7 (minor), 24.6 (major), 23.4 (minor), 23.3 (major), 23.2 (major and minor)

TLC R_f = 0.41 (3 elutions with 50% toluene/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



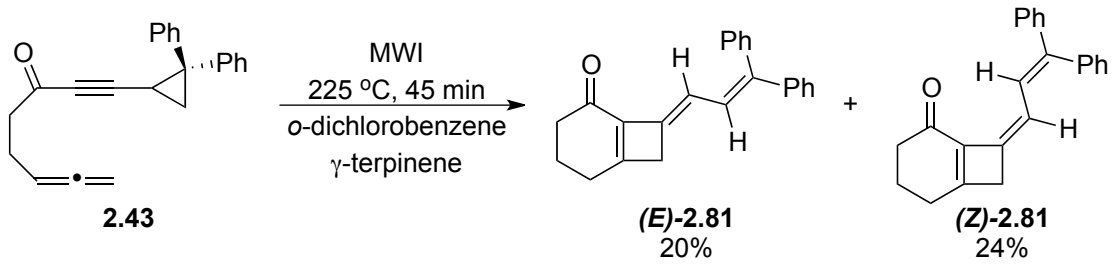
2.42 **2.78**, 66%

8-Cyclopropylbicyclo[4.2.0]octa-1(8),5-dien-2-one (2.78). A NMR tube was charge with the allene-ynone **2.42** (9 mg, 0.06 mmol), 1,4-dimethoxybenzene (1.2 mg, 9 x 10^{-3} mmol), and 1,2-dichlorobenzene (0.5 mL). A ^{1}H NMR of the starting material was acquired (16 scans, 12 s delay time). The solution was then transferred to a Biotage™ microwave vial. The vial was capped and the solution was irradiated in the microwave for 30 min at 225 °C. The reaction mixture was then transferred to an NMR tube and a ^{1}H NMR of the crude mixture was acquired (16 scans, 12 s delay time). Based on the NMR, the only product obtained was alkylidene cyclobutene **2.78** in a 66% yield. The yield was determined by integration of the cyclopropane protons of the starting material and product in relation to the internal standard.

Data for **2.78**: (JMO3-194)

^{1}H NMR (300 MHz, $C_6D_4Cl_2$)

δ 5.07 (t, *J* = 3.6 Hz, 1H), 2.86 (s, 2H), 2.51 – 2.42 (m, 4H), 1.82 – 1.74 (m, 2H), 0.95 – 0.91 (m, 4H)



2.43 ***(E)*-2.81** 20% ***(Z)*-2.81** 24%

(8E) and (8Z)-8-(3,3-diphenylallylidene)bicyclo[4.2.0]oct-1(6)-en-2-one (2.81). A 2-5 mL Biotage microwave vial was charged with allene-ynone **2.43** (33 mg, 0.106 mmol), 1,2-dichlorobenzene (1.8 mL), and γ-terpinene (3.4 mL, 21.3 mmol). The vial was capped with a Reseal™ septum and irradiated in the microwave for 45 min at 225 °C. This procedure was repeated two times for a total of 99 mg of allene-ynone **2.43**. The combined reaction mixtures were diluted with hexanes (10 mL) and applied to a silica gel column. The column was eluted with hexanes (200 mL) then a gradient of 10% - 25% ethyl acetate/hexanes. Two products were isolated and revealed as ***E*-2.81** (19.5 mg, 20%) and ***Z*-2.81** (23.7 mg, 24%) both appearing as lightly colored oils. In addition to the reported data, COSY and HMQC spectra were also acquired and can be found in Appendix A. The stereochemical assignment was not confirmed experimentally, but was assigned by comparison with spectra as predicted by Spartan '08 (see Appendix A).

Data for ***E*-2.81**: (JMO4-72)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.41 (t, *J* = 7.7 Hz, 2H), 7.36 (t, *J* = 7.0 Hz, 1H), 7.32 – 7.28 (m, 4H), 7.27 – 7.24 (m, 3H), 6.64 (d, *J* = 11.9 Hz, 1H), 6.28 (d, *J* = 11.2 Hz, 1H), 3.38 (s, 2H), 2.57 (t, *J* = 5.6 Hz, 2H), 2.39 (t, *J* = 6.3 Hz, 2H), 2.17 (p, *J* = 5.6 Hz, 2H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 191.7, 173.2, 142.9, 142.8, 141.8, 139.6, 137.4, 130.4 (2C), 128.3 (2C), 128.2 (2C), 127.5 (2C), 127.4, 127.2, 124.0, 114.6, 38.9, 38.1, 25.9, 24.1

IR (thin film)

3361, 2923, 1661 cm^{-1}

MS EI+

m/z (%) 336 (15), 335 (55), 332 (100), 320 (10), 292 (8), 260 (12)

HRMS TOF MS ES+: $C_{23}H_{20}ONa$

Calculated: 335.1412 Found: 335.1392

TLC R_f = 0.27 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

Data for ***Z*-2.81**: (JMO4-72)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.9 (d, *J* = 11.2 Hz, 1H), 7.46 – 7.43 (m, 4H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.33 (t, *J* = 7.0 Hz, 2H), 7.29 (d, *J* = 7.7 Hz, 2H), 7.25 (t, *J* = 7.0 Hz, 1H) 5.71 (d, *J* = 11.9 Hz, 1H), 3.16 (s, 2H), 2.54 (t, *J* = 5.6 Hz, 2H), 2.49 (t, *J* = 6.3 Hz, 2H), 2.20 (p, *J* = 6.3 Hz, 2H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 191.3, 174.9, 143.5, 141.9, 140.8, 140.1, 137.4, 130.6 (2C), 128.24 (2C), 128.23 (2C), 127.2 (2C), 127.1, 127.0, 126.8, 115.2, 40.1, 38.1, 25.9, 24.1

IR (thin film)

3055, 3023, 2924, 1677 cm^{-1}

MS EI+

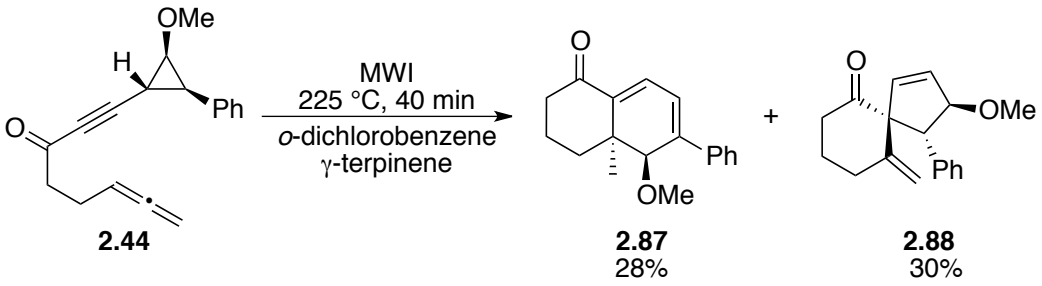
m/z (%) 335 (100), 330 (30), 328 (30), 288 (30), 229 (33), 227 (50), 225 (70), 217 (20)

HRMS TOF MS ES+: $C_{23}H_{20}ONa$

Calculated: 335.1412 Found: 335.1399

TLC R_f = 0.36 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

Other See Appendix A for the COSY Spectrum, HMQC Spectrum, and a Spartan predicted ^{1}H NMR spectrum



2.44 **2.87** 28% **2.88** 30%

2.87 and 2.88. A 2-5 mL Biotage™ microwave vial was charged with the allene-ynone **2.44** (40 mg, 0.15 mmol), 1,2-dichlorobenzene (1.5 mL), and γ-terpinene (3.6 mL). The vial was capped and the solution was irradiated in the microwave for 40 min at 225 °C. The reaction mixture was directly applied to a silica gel column and eluted with hexanes (100 mL) followed by a gradient of 5% ethyl acetate/hexanes to 20% ethyl acetate/hexanes. Two products were isolated from the column chromatography **2.87** (11 mg, 28%) and **2.88** (12 mg, 30%). The stereochemical assignment was not determined experimentally, however the assignments were made by comparison of the experimental spectra to spectra computed by Spartan '08 (See Appendix A).

Data for **2.87**: (JMO5-88)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.62-7.60 (m, 2H), 7.45-7.43 (m, 2H), 7.39-7.38 (m, 1H), 7.12 (dd, *J* = 6.0, 0.5 Hz, 1H), 6.68 (dd, *J* = 6.0, 0.3 Hz, 1H), 4.06 (s, 1H), 3.22 (s, 3H), 2.67-2.63 (m, *J*

= 2.2 Hz, 1H), 2.41-2.35 (m, 2H), 2.10-2.01 (m, 3H), 1.69-1.66 (m, *J* = 2.6 Hz, 1H), 1.14 (s, 3H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 199.4, 140.8, 140.1, 139.5, 128.8 (2C), 128.4, 128.2, 126.0 (2C), 122.2, 81.2, 57.0, 40.1, 39.8, 29.4, 22.4, 17.8

IR (thin film)

2929, 2822, 1671, 1618, 1545 cm^{-1}

MS EI+

m/z (%) 268 (22), 105 (34), 97 (34), 91 (24), 83 (44), 81 (57), 73 (47), 71 (45), 69 (69), 60 (44)

HRMS EI+ $C_{18}H_{20}O_2$

Calculated: 268.1463 Found: 268.1467

TLC R_f = 0.12 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

Other See Appendix A for COSY, HMQC, and HMBC spectra

Data for **2.88**: (JMO5-88)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.31 – 7.23 (m, 5H), 6.24 (dd, *J* = 1.4, 6.3 Hz, 1H), 5.89 (dd, *J* = 1.4 Hz, 6.3 Hz, 1H), 4.92 (s, 1H), 4.85 (s, 1H), 4.65 (dd, *J* = 1.4, 4.2 Hz, 1H), 3.28 (d, *J* = 5.6 Hz, 1H), 3.21 (s, 3H), 2.51 – 2.49 (m, 1H), 2.41 (ddd, *J* = 6.3, 13.3, 14.7 Hz, 1H), 2.00 (d, *J* = 14.7 Hz, 1H), 1.75 – 1.71 (m, 1H), 1.51 – 1.44 (m, 1H), 1.10 – 1.05 (m, 1H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 211.4, 148.4, 139.7, 135.7, 132.5, 129.5 (2H), 128.3 (2H), 127.3, 113.8, 92.1, 72.4, 60.0, 57.1, 40.0, 32.9, 23.9

IR (thin-film)

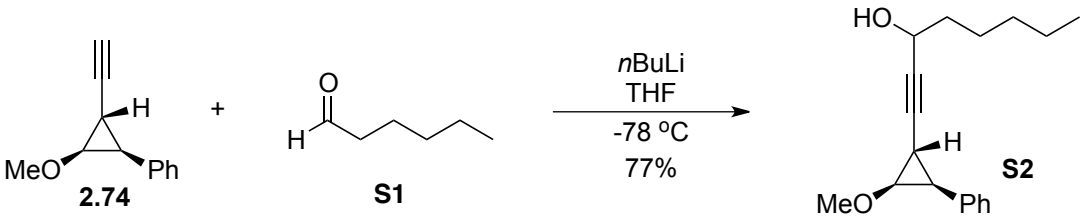
2932, 2869, 1707 cm^{-1}

HRMS EI-HRMS: $C_{18}H_{20}O_2Na$

Calculated: 291.1361 Found: 291.1352

TLC R_f = 0.22 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

Representative Preparation of the Control Substrates



1-(2-Methoxy-3-phenylcyclopropyl)oct-1-yn-3-ol (S2). A flame-dried one-dram vial under a nitrogen atmosphere was charged with alkyne **2.74** (25 mg, 0.145 mmol) and tetrahydrofuran (0.15 mL). The solution was cooled to -78 °C and *n*-butyllithium (0.10 mL of a 1.6 M hexanes solution, 0.160 mmol) was added via syringe. The reaction was maintained at -78 °C for 45 min at which time hexanal (**S1**) (17.4 μL, 0.145 mmol) was added via syringe. The reaction was maintained at -78 °C for 15 min and was then warmed to rt over 1 h at which time all starting material had been consumed based on TLC. The reaction was quenched with saturated aqueous ammonium chloride (0.2 mL) and water (0.2 mL) then diluted with ethyl acetate (0.5 mL). The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 0.5 mL). The combined organic layers were washed with brine (0.5 mL) and dried by passing through a pipet packed with anhydrous sodium sulfate. The crude material was subjected to silica gel flash chromatography eluting with 15% ethyl acetate/hexanes. The fractions containing the desired

product were concentrated under reduced pressure to provide 31 mg of **S2** as a colorless oil in 77% yield. The title compound **S2** was produced as an inseparable mixture (by column chromatography) of diastereomers and could not be differentiated by TLC, ^{1}H NMR, or ^{13}C NMR, but could be differentiated after allene formation.

Data for **S2:** (JMO4-100)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.34 – 7.20 (m, 5H), 4.38 (ddt, *J* = 1.5, 6.6, 6.6 Hz, 1H), 3.63 (dd, *J* = 3.3, 6.9 Hz, 1H), 3.30 (s, 3H), 2.33 (t, *J* = 6.6 Hz, 1H), 1.90 – 1.86 (m, 2H), 1.73 – 1.65 (m, 2H), 1.51 – 1.43 (m, 2H), 1.39 – 1.30 (m, 4H), 0.93 (t, *J* = 3.6 Hz, 3H)

^{13}C NMR δ 135.3, 128.08 (2C), 128.05 (2C), 126.4, 84.7, 79.1, 66.5, 62.7, 58.4, 38.0, 33.1, 31.4, 24.8, 22.5, 15.2, 14.0

IR (thin film)

3383, 3028, 2932, 2859, 2233, 1603 cm^{-1}

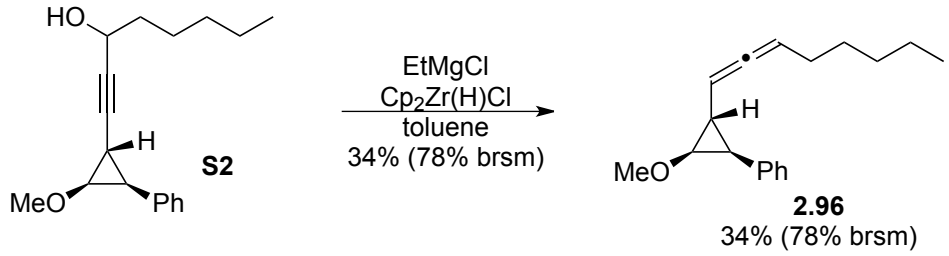
MS EI+

m/z (%) 272 (25), 169 (64), 141 (100), 134 (37), 128 (40), 115 (50), 91 (82)

HRMS EI-HRMS: $C_{18}H_{24}O_2$

Calculated: 272.1776 Found: 272.1764

TLC R_f = 0.26 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-(2-Methoxy-3-(octa-1,2-dienyl)cyclopropyl)benzene (2.96). A flame dried 5 mL round bottomed flask under a nitrogen atmosphere was charged with the propargyl alcohol **S2** (28 mg, 0.101 mmol) and toluene (0.51 mL). The solution was cooled to 0 °C and ethyl magnesium chloride (51 μL of a 2 M solution in ether, 0.101 mmol) was added via syringe. The reaction was maintained at 0 °C for 10 min and was then warmed to rt and stirred 10 min more. Zirconocene chloride hydride (29 mg, 0.111 mmol) was added in one portion and the flask was wrapped in aluminum foil and left to stir overnight. The reaction mixture was diluted with ether (1 mL) and filtered through celite. The celite pad was washed with ether and the filtrate was transferred to a separatory funnel containing saturated aqueous sodium bicarbonate solution (3 mL). The aqueous layer was extracted with ether (2 x 2 mL). The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by silica gel flash chromatography eluting with 10% toluene/hexanes. The fractions containing the desired product were concentrated under reduced pressure to provide 9 mg of the title compound **2.96** in a 34% yield (78% BRSM) as a 1.1:1 mixture of diastereomers as a colorless oil.

Data for **2.96**: (JMO4-106)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.32 – 7.17 (m, 5H, major and minor), 5.33 – 5.22 (m, 2H, major and minor), 3.38 (dd, *J* = 3.3, 6.9 Hz, 1H, minor), 3.37 (dd, *J* = 3.3, 6.6 Hz, 1H, major), 3.21 (s, 3H, major), 3.21 (s, 3H, minor), 2.09 – 1.97 (m, 3H, major and minor), 1.88 – 1.81 (m, 1H, major and minor), 1.44 – 1.40 (m, 2H, major and minor), 1.38 – 1.31 (m, 4H, major and minor), 0.94 – 0.88 (m, 3H, major and minor)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 203.5 (minor), 203.4 (major), 137.2 (major and minor), 127.9 (4C, major and minor), 125.7 (major and minor), 93.9 (major and minor), 91.4 (major and minor), 67.2 (major), 67.1 (minor), 58.2 (major and minor), 31.9 (minor), 31.8 (major), 29.7 (major and minor), 28.9 (major and minor), 28.8 (major and minor), 24.7 (minor), 24.5 (major), 22.5 (major and minor), 14.1 (major and minor)

IR (thin film)

2956, 2927, 2854, 1958, 1603 cm^{-1}

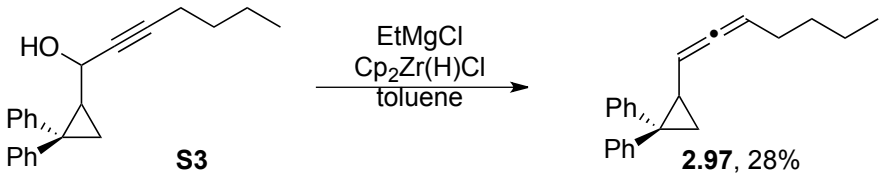
MS EI+

m/z (%) 256 (16), 185 (92), 147 (100), 115 (30), 91 (27)

HRMS EI-HRMS: $C_{18}H_{24}O$

Calculated: 256.1827 Found: 256.1823

TLC R_f = 0.2 (10% toluene/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



(2-(hepta-1,2-dien-1-yl)cyclopropane-1,1-diyl)dibenzene (2.97). A 5 mL round bottomed flask was charged with propargyl alcohol **S3** (50 mg, 0.164 mmol) and toluene (0.82 mL). The reaction, under a nitrogen atmosphere, was cooled to 0 °C at which time ethylmagnesium bromide (0.091 mL of a 2 M solution in ether, 0.181 mmol) was added dropwise. The reaction was maintained at 0 °C for 10 min then warmed to rt and allowed to stir an additional 10 min. Zirconocene chloride hydride (51 mg, 0.197 mmol) was then added in one portion and the reaction was left to stir at rt overnight. The reaction was quenched by adding saturated aqueous sodium bicarbonate (1 mL). The layers were separated and the aqueous layer was extracted with

ether (3 x 1 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered through a plug of silica (30% ethyl acetate/hexanes eluant) and concentrated. The crude material was purified by silica gel flash chromatography eluting with 4% ethyl acetate/hexanes to provide 13.2 mg of **2.97** in a 28% yield.

Data for **2.97** (JMO3-71)

^{1}H NMR (300 MHz, C_6D_6)

δ 7.31-7.29 (m 2H), 7.14-6.97 (m, 8H), 5.18 (ddt, *J* = 1.2, 6.9, 6.9 Hz, 1H), 4.88 (ddt, *J* = 2.7, 5.7, 7.8 Hz, 1H), 2.24-2.16 (m, 1H), 1.73-1.65 (m, 2H), 1.41 (dt, *J* = 5.1, 15.6 Hz, 2H), 1.28-1.15 (m, 4H), 0.86-0.81 (m, 3H)

^{13}C NMR δ 204.4, 146.7, 141.2, 131.3, 128.21, 128.17, 127.2, 126.4, 125.7, 92.5, 91.5, 37.3, 31.5, 28.5, 26.4, 22.1, 21.2, 13.9

IR 3058, 2957, 2926, 1957 cm^{-1}

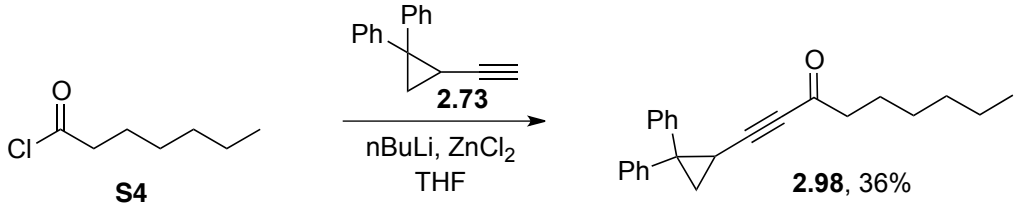
MS EI+

m/z (%) 288 (20), 202 (20), 191 (35), 167 (35), 165 (95), 152 (35), 115 (75), 91 (100), 77 (40)

HRMS TOF MS ES+: $C_{22}H_{24}$

Calculated: 288.1878 Found: 288.1877

TLC R_f = 0.73 (20% ethyl acetate/hexanes) [Silica gel, UV]



1-(2,2-Diphenylcyclopropyl)non-1-yn-3-one (2.98). A flame-dried, 5 mL pear-shaped flask under an argon atmosphere was charged with alkyne **2.73** (104 mg, 0.476 mmol) and tetrahydrofuran (0.64 mL). The solution was cooled to -78 °C at which time *n*-butyllithium (0.30 mL of a 1.6 M hexanes solution, 0.476 mmol) was added dropwise. The reaction was maintained at -78 °C for 30 min and was then warmed to 0 °C. In a second 5 mL round bottomed flask under an argon atmosphere, freshly fused zinc chloride (57.4 mg, 0.421 mmol) was dissolved in tetrahydrofuran (0.42 mL). This solution was cooled to 0 °C and the solution of lithium acetylide was added via cannula. The reaction was maintained at 0 °C for 30 min and was then cooled to -10 °C. Heptanoyl chloride (**S4**) (52.5 μL, 0.340 mmol) was then added via syringe and the reaction was allowed to warm to 0 °C and stir at that temperature for 1 h. Saturated aqueous ammonium chloride solution (2 mL) was then added and the mixture was poured into a separatory funnel containing ether (5 mL) and water (5 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography eluting with 5% ethyl acetate/ hexanes to afford 40 mg of ynone **2.98** as a colorless oil in 36% yield.

Data for **2.98**: (JMO4-62)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.43 – 7.39 (m, 2H), 7.35 – 7.30 (m, 2H), 7.28 – 7.17 (m, 6H), 2.32 (dd, J = 5.7, 9.0 Hz, 1H), 2.12 (t, *J* = 7.2 Hz, 2H), 1.90 (dd, *J* = 5.7, 4.8 Hz, 1H), 1.80 (dd, 4.8, 9.0 Hz, 1H), 1.35 – 1.21 (m, 4H), 1.20 – 1.13 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 188.3, 143.7, 140.1, 130.0 (2C), 128.6 (2C), 128.3 (2C), 128.0 (2C), 127.2, 126.9, 95.0, 81.8, 45.3, 40.0, 31.4, 28.6, 24.0, 23.9, 22.5, 15.7, 14.1

IR (thin film)

3058, 3026, 2954, 2927, 2856, 2201, 1667 cm^{-1}

MS EI+

m/z (%) 354 (35), 353 (100), 335 (10), 330 (5), 305 (8), 289 (8), 261 (5), 227 (9), 217 (9)

HRMS TOF MS ES+: $C_{24}H_{26}ONa$

Calculated: 353.1881 Found: 353.1862

TLC R_f = 0.56 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

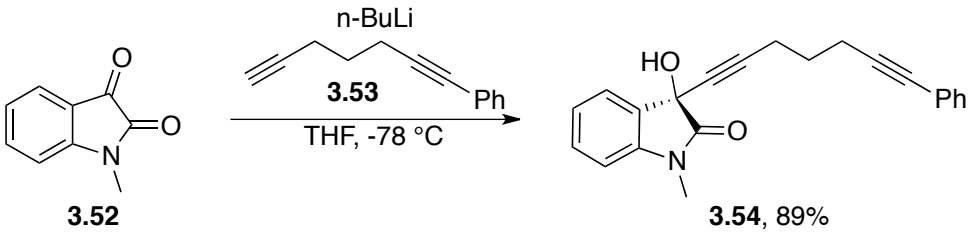
4.2 PREPARATION OF THE COMPOUNDS DESCRIBED IN CHAPTER 3

4.2.1 General Methods

Unless otherwise noted, all reactions were performed in flame-dried glassware under an inert atmosphere of dry nitrogen. All commercially available compounds were purchased from Aldrich Chemical Co., GFS Chemicals, Strem Chemicals, Acros Organics, and Advanced Chemtech and used as received. The reaction solvents tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were purified by passing through alumina using the Sol-Tek ST-002 solvent purification system. Triethylamine (NEt_3) and toluene and 1,2-dichlorobenzene were freshly distilled from CaH_2 prior to use. Benzene was freshly distilled from sodium/benzophenone prior to use. Purification of the compounds by flash column

chromatography was performed using silica gel (32-63 μm particle size, 60 Å pore size) purchased from Silicycle. TLC analyses were performed on EMD Chemicals Silica Gel 60 F_{254} glass plates (250 μm thickness). ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Avance 300 MHz, 500 MHz, or 700 MHz spectrometers. Spectra were referenced to residual chloroform (7.26 ppm, ^{1}H, 77.0 ppm, ^{13}C), benzene (7.16 ppm, ^{1}H, 128.0 ppm, ^{13}C), or *o*-dichlorobenzene (6.93 ppm, ^{1}H, 127.19 ppm, ^{13}C). Chemical shifts are reported in ppm, multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quin. (quintet), and m (multiplet). Coupling constants, *J*, are reported in hertz. All NMR spectra were obtained at room temperature unless otherwise specified. IR spectra were obtained using a Nicolet Avatar E.S.P. 360 FT-IR. EI mass spectroscopy was performed on a Micromass Autospec high-resolution mass spectrometer. Melting points are uncorrected and were determined using a Mel-Temp instrument. All microwave-mediated reactions were carried out using a Biotage Initiator™ Exp microwave synthesizer unless otherwise noted. The microwave parameters were set to variable power, constant temperature, with the fixed hold time set to on. The microwave reactions were carried out in 0.2-0.5 mL, 0.5-2 mL, or 2-5 mL Biotage™ microwave vials.

4.2.2 Detailed Experimental Protocols



3.52 **3.54**, 89%

3-hydroxy-1-methyl-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-2-one (3.54). A flame-dried single necked 10 mL round bottomed flask under a nitrogen atmosphere was charged with diyne

3.53 (0.133 g, 0.792 mmol) and tetrahydrofuran (4 mL) and cooled to -78 °C. To this solution was added *n*-butyllithium (0.50 mL of a 1.6 M hexanes solution, 0.79 mmol) dropwise over a period of 5 min. The reaction was maintained at -78 °C for 1 h at which time *N*-methylisatin (**7**) (0.116 g, 0.720 mmol) in tetrahydrofuran (1.5 mL) was added dropwise over 5 min. The reaction was maintained at -78 °C for 30 min and was then allowed to warm to rt and stirred overnight at which time all starting material had been consumed based on TLC. The reaction was quenched with saturated aqueous ammonium chloride solution (2 mL). The aqueous phase was separated and extracted with ether (3 x 2 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with 30% ethyl acetate/hexanes to afford 0.211 g of propargyl alcohol **3.54** in 89% yield as a light orange solid.

Data for **3.54**: (JMO3-78)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.55 – 7.52 (m, 1 H), 7.38 – 7.32 (m, 3H), 7.28 – 7.24 (m, 3H), 7.13 (dt, *J* = 0.9, 7.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.50 – 3.47 (m, 1H), 3.21 (s, 3H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.80 (p, *J* = 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 174.3, 142.8, 131.4 (2C), 130.1, 129.4, 128.0 (2C), 127.5, 124.3, 123.6, 123.5, 108.6, 88.9, 86.5, 81.1, 77.6, 69.0, 27.3, 26.4, 18.4, 18.0

IR (thin film)

3350, 3057, 2937, 2905, 2235, 1961, 1896, 1711, 1614 cm^{-1}

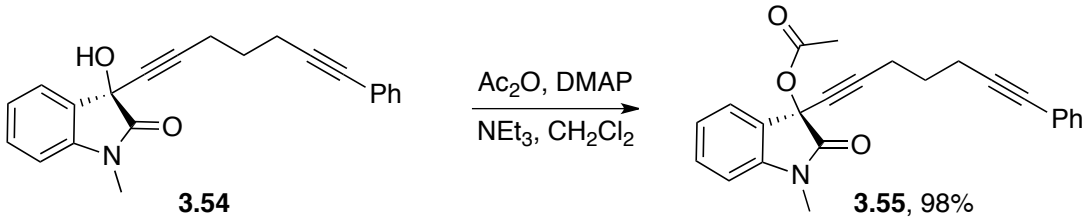
MS EI+

m/z (%) 329 (22), 328 (13), 314 (46), 252 (14), 224 (37), 129 (17), 128 (50), 116 (20), 115 (100)

HRMS EI-HRMS: $C_{22}H_{18}NO_2$

Calculated 329.1416; Found 329.1414

TLC R_f = 0.44 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-methyl-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-3-yl acetate (3.55). A flame-dried 5 mL round bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **3.54** (0.200 g, 0.607 mmol) and dichloromethane (1.9 mL). 4-Dimethylaminopyridine (7.4 mg, 0.0607 mmol) was added followed by triethylamine (304 μL, 2.19 mmol) and finally acetic anhydride (137 μL, 1.45 mmol). The reaction was allowed to stir at room temperature for 1 h at which time complete consumption of the starting material was observed by TLC. Saturated aqueous sodium bicarbonate solution (1 mL) was added to quench the reaction. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 1 mL). The combined organic layers were washed with brine (2 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography eluting with 30% ethyl acetate/hexanes to provide 0.220 g of propargyl acetate **3.55** in 98% yield as a colorless oil.

Data for **3.55**: (JMO3-80)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.43 (d, J = 7.2 Hz, 1H), 7.38 – 7.33 (m, 3H), 7.28 – 7.26 (m, 3H), 7.09 (t, J = 7.5 Hz, 1H), 6.85 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.47 (t, J = 6.9 Hz, 2H), 2.43 (t, J = 7.2 Hz, 2H), 2.09 (s, 3H), 1.81 (p, J = 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 170.7, 168.4, 143.4, 131.4 (2C), 130.3, 128.1 (2C), 127.5, 127.0, 123.5, 123.4, 123.1, 108.6, 88.7, 88.3, 81.2, 74.1, 73.1, 27.1, 26.7, 20.6, 18.5, 18.1

IR (thin film)

3058, 2937, 2836, 2244, 1739, 1614 cm^{-1}

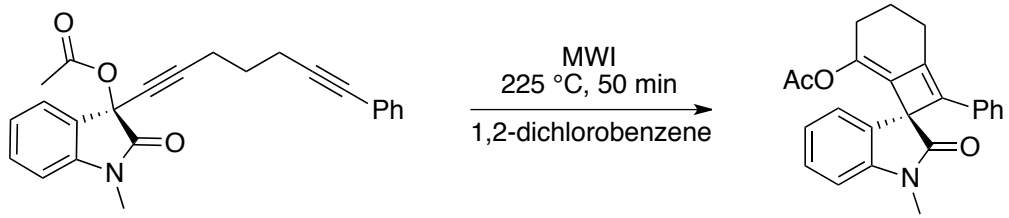
MS EI+

m/z (%) 371 (8), 330 (72), 329 (100), 314 (71), 312 (90), 301 (95), 300 (88), 273 (86), 272 (82), 252 (85), 225 (75), 184 (75), 183 (94), 115 (83)

HRMS EI-HRMS: $C_{24}H_{21}NO_3$

Calculated 371.1521; Found 371.1520

TLC R_f = 0.22 (30% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.55 **3.58**, 60%

1'-methyl-2'-oxo-8-phenylspiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl acetate (3.58). In a 0.5 – 2 mL Biotage™ microwave vial, propargyl acetate **3.55** (30 mg, 0.081mmol) was dissolved in 1,2-dichlorobenzene (1.6 mL). The vial was capped and the solution was irradiated in the microwave for 30 min at 225 °C (time does not include a *ca*. 4 min ramp time).

The reaction mixture was diluted with hexanes (2 mL) and applied to a silica gel column. The column was eluted with hexanes (100 mL), then eluted with 25% ethyl acetate/hexanes. The fractions containing the desired product were concentrated under reduced pressure to provide 18 mg of spirooxindole **3.58** in 60% yield as a brown oil.

Data for **3.58**: (JMO3-86)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.29 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 2H), 7.08 (t, *J* = 7 Hz, 1H), 6.98 (t, *J* = 7.7 Hz, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 2H), 3.34 (s, 3H), 2.79 – 2.67 (m, 2H), 2.42 – 2.34 (m, 2H), 2.17 – 2.03 (m, 2H), 1.77 (s, 3H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 175.5, 167.3, 147.0, 143.8, 137.7, 132.7, 132.0, 128.54 (2C), 128.47, 127.6, 127.1, 125.4 (2C), 124.5, 123.5, 122.4, 107.8, 61.8, 27.3, 26.7, 23.7, 22.3, 20.5

IR (thin film)

3055, 2932, 1761, 1717, 1611 cm^{-1}

MS EI+

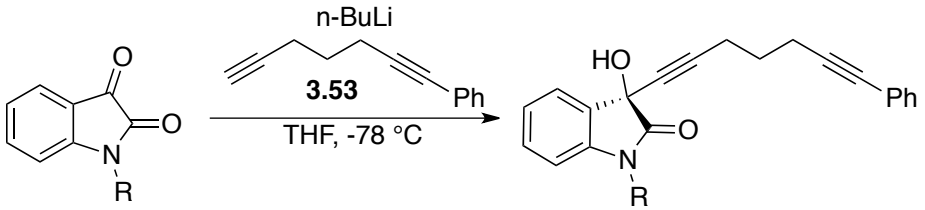
m/z (%) 372 (16), 371 (73), 330 (30), 329 (100), 328 (78), 300 (10), 288 (7), 272 (13), 244 (10), 202 (9), 105 (12), 77 (9)

HRMS EI-HRMS: $C_{24}H_{21}NO_3$

Calculated 371.1521; Found 371.1532

TLC R_f = 0.14 (25% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

Other COSY, HMBC, HMQC, and DEPT-135 spectra for **3.58** are attached in Appendix A.



3.61 R = MOM
3.62 R = SEM
3.63 R = Boc

3.64 R = MOM, 75%
3.65 R = SEM, 83%
3.66 R = Boc, 33%

General Procedure 1

3-hydroxy-1-(methoxymethyl)-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-2-one (3.64). A 50 mL flame dried round bottomed flask under a nitrogen atmosphere was charged with diyne **3.53** (0.484 g, 2.88 mmol) and tetrahydrofuran (11.5 mL). The solution was cooled to 0 °C and *n*-butyllithium (1.8 mL of a 1.6 M hexanes solution, 2.88 mmol) was added dropwise via syringe. The reaction was maintained at 0 °C for 15 min at which time *N*-MOM isatin **3.61** (0.500 g, 2.62 mmol) was added over 5 min as a solution in tetrahydrofuran (8 mL). The reaction was warmed to rt and was left to stir for 2 h at which time all starting material had been consumed based on TLC. Saturated aqueous ammonium chloride (10 mL) and water (5 mL) were added to quench the reaction. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude material was purified by silica gel flash chromatography eluting with 30% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide 0.708 g of propargyl alcohol **3.64** in75% yield as an orange oil.

Data for **3.64**: (JMO5-16)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.57 (d, *J* = 6.6 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.28 – 7.26 (m, 3H), 7.17 (t, *J* = 7.5 Hz, 1H), 7.05 (d, *J* = 7.8, 1H), 5.16 (d, *J* = 10.8 Hz, 1H), 5.11 (d, *J* = 11.1 Hz,

1H), 3.85 (s, 1H), 3.36 (s, 3H), 2.48 (t, J = 6.9 Hz, 2H), 2.41 (t, J = 7.2 Hz, 2H), 1.80 (p, J = 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 174.8, 141.1, 131.5 (2C), 130.4, 128.7, 128.2 (2C), 127.6, 124.6, 124.1, 123.6, 110.2, 88.8, 87.2, 81.3, 77.2, 71.7, 69.4, 56.3, 27.3, 18.5, 18.0

IR (thin film)

3374, 2938, 2234, 1723, 1614, 1488 cm^{-1}

MS TOF MS ES+

m/z (%) 383 (30), 382 (100), 365 (17), 227 (15)

HRMS TOF MS ES+: $C_{23}H_{21}NO_3Na$

Calculated: 382.1419 Found: 382.1391

TLC R_f = 0.08 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

3-hydroxy-3-(7-phenylhepta-1,6-diyn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl) indolin-2-one (3.65). Following General Procedure 1: Diyne **3.53** (167 mg, 0.992 mmol) and tetrahydrofuran (4 mL) were cooled to -78 °C. To this solution was added *n*-butyllithium (0.62 mL of a 1.6 M solution in hexanes, 0.992 mmol). The reaction was maintained at -78 °C for 30 min at which time SEM-isatin **3.62** (250 mg, 0.902 mmol) was added as a solution in tetrahydrofuran (1.8 mL). The reaction was warmed to room temperature and left to stir for 3 h. The crude material was purified by silica gel flash chromatography eluting with 20% ethyl acetate/hexanes to provide 335 mg of propargyl alcohol **3.65** as a yellow oil in 83% yield.

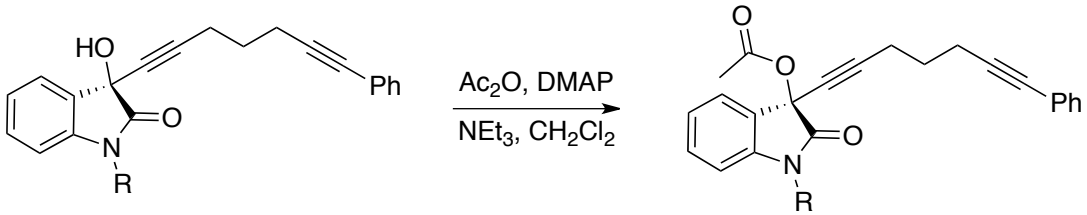
Data for **3.65**: (JMO4-162)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.54 (dt, *J* = 7.5, 0.6 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.29 – 7.25 (m, 3H), 7.16 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 5.18 (d, *J* = 11.1 Hz, 1H), 5.12 (d, *J* = 10.8 Hz, 1H), 3.62 – 3.56 (m, 2H), 3.19 – 3.15 (m, 1H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.80 (p, *J* = 6.9 Hz, 2H), 0.94 – 0.89 (m, 2H), -0.04 (s, 9H)

TLC R_f = 0.30 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

***tert*-butyl 3-hydroxy-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indoline-1-carboxylate (3.66).** Following General Procedure 1: Diyne **3.53** (299 mg, 1.78 mmol) and tetrahydrofuran (9 mL) were cooled to -78 °C. To this solution was added *n*-butyllithium (1.11 mL of a 1.6 M solution in hexanes, 1.78 mmol). The reaction was maintained at -78 °C for 1 h at which time Boc-isatin **3.63** (400 mg, 1.62 mmol) was added as a solution in tetrahydrofuran (3.2 mL). The reaction was warmed to room temperature and left to stir for 2 h. The crude material was purified by silica gel flash chromatography eluting with 35% ethyl acetate/hexanes to provide 225 mg of impure propargyl alcohol **3.66** in 33% yield. The impure alcohol **3.66** was carried on to the acetylation protocol without further purification.



3.64 R = MOM
3.65 R = SEM
3.66 R = Boc

3.67 R = MOM, 91%
3.68 R = SEM, 98%
3.69 R = Boc, 66%

General Procedure 2

1-(methoxymethyl)-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-3-yl acetate (3.67). A flame dried 25 mL round bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **3.64** (0.660 g, 1.84 mmol) and dichloromethane (7.4 mL). To this solution was added 4-dimethylaminopyridine (23 mg, 0.184 mmol), followed by triethylamine (0.92 mL, 6.62 mmol), and finally acetic anhydride (0.42 mL, 4.42 mmol). The reaction was left to stir at rt for 2 h at which time all starting material had been consumed based on TLC. The reaction was quenched by adding saturated aqueous sodium bicarbonate solution (8 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and concentrated. The crude material was purified by silica gel flash chromatography eluting with a gradient of 15 – 20% ethyl acetate/hexanes to afford 0.670 g of propargyl acetate **3.67** in 91% yield.

Data for **3.67**: (JMO5-22)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.39 – 7.34 (m, 3H), 7.29 – 7.27 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 5.15 (d, *J* = 11.1 Hz, 1H), 3.43 (s, 3H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 1.82 (p, *J* = 6.9 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.3, 168.5, 141.6, 131.4 (2C), 130.4, 128.1 (2C), 127.6, 126.6, 123.7, 123.5, 123.2, 110.2, 88.8, 88.6, 81.3, 74.2, 73.4, 72.0, 56.5, 27.1, 20.6, 18.5, 18.1

IR (thin film)

3058, 2938, 2831, 2243, 1746, 1613, 1488 cm^{-1}

MS TOF MS ES+

m/z (%) 527 (43), 492 (30), 440 (20), 425 (70), 424 (100), 397 (20), 382 (15), 381 (18)

HRMS TOF MS ES+: $C_{25}H_{23}NO_4Na$

Calculated: 424.1525 Found: 424.1564

TLC R_f = 0.24 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-3-yl acetate (3.68). Following General Procedure 2: To a solution of propargyl alcohol **3.65** (330 mg, 0.741 mmol) and dichloromethane (2.3 mL) was added 4-dimethylaminopyridine (9.1 mg, 0.0741 mmol), triethylamine (370 μL, 2.67 mmol), and acetic anhydride (168 μL, 1.78 mmol). The reaction was complete within 1 h. The residue was purified via silica gel flash chromatography eluting with 16% ethyl acetate/hexanes to provide 361 mg of propargyl acetate **3.68** in 98% yield as a lightly colored oil.

Data for **3.68**: (JMO4-166)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.45 – 7.42 (m, 1H), 7.40 – 7.35 (m, 3H), 7.30 – 7.26 (m, 3H), 7.15 – 7.09 (m, 2H), 5.25 (d, *J* = 11.4 Hz, 1H), 5.18 (d, *J* = 11.1 Hz, 1H), 3.74 (ddd, *J* = 6.9, 9.9, 9.9 Hz, 1H), 3.64 (ddd, *J* = 6.9, 9.9, 9.9 Hz, 1H), 2.48 (t, *J* = 6.9 Hz, 2H), 2.44 (t, *J* = 7.2 Hz, 2H), 2.10 (s, 3H), 1.82 (p, *J* = 6.9 Hz, 2H), 1.04 – 0.88 (m, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.1, 168.3, 141.9, 131.4, 130.3, 128.1, 127.6, 126.7, 123.59, 123.53, 123.2, 110.3, 88.6, 81.3, 76.9, 74.3, 73.4, 69.9, 66.0, 27.2, 20.6, 18.5, 18.1, 17.6, -1.5

IR (thin film)

3058, 2951, 2897, 2244, 1747, 1614 cm^{-1}

MS TOF MS ES+

m/z (%) 516 (22), 511 (45), 510 (100), 482 (35), 431 (32), 365 (30), 363 (28), 227 (41)

HRMS TOF MS ES+: $C_{29}H_{33}NO_4SiNa$

Calculated: 510.2077 Found: 510.2053

TLC R_f = 0.44 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

***tert*-butyl 3-acetoxy-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indoline-1-carboxylate (3.69).** Following General Procedure 2: To a solution of propargyl alcohol **3.66** (200 mg, 0.482 mmol) and dichloromethane (1.6 mL) was added 4-dimethylaminopyridine (5.9 mg, 0.0482 mmol), triethylamine (241 μL, 1.74 mmol), and acetic anhydride (109 μL, 1.16 mmol). The reaction was complete within 2 h. The residue was purified via silica gel flash chromatography eluting with a gradient of 15-20% ethyl acetate/hexanes to provide 146 mg of propargyl acetate **3.69** in 66% yield.

Data for **3.69**: (JMO9-188)

^{1}H NMR (300 MHz, $CDCl_3$) Reported resonances correspond to the major rotational isomer or a mixture. The minor rotational isomer chemical shift is not reported.

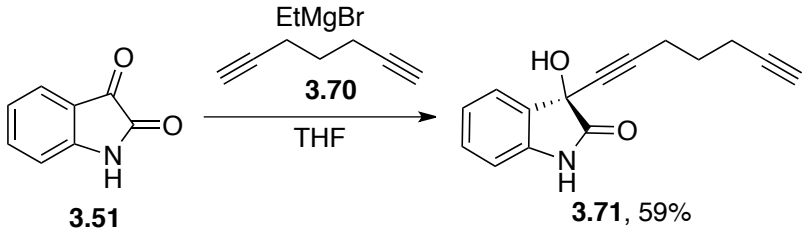
δ 7.92 (d, *J* = 8.1 Hz, 1H), 7.47-7.39 (m, 3H), 7.31-7.30 (m, 4H), 7.25-7.20 (m, 1H), 2.52-2.45 (m, 4H), 2.12 (s, 3H), 1.89-1.80 (m, 2H), 1.68 (s, 9H) .

MS *m/z* (%)

480 (10), 380 (10), 321 (10), 320 (100), 298 (10)

HRMS TOF MS ES+ $C_{28}H_{27}NO_5Na$

Calculate: 480.1787; Found: 480.1788



3.51 **3.71**, 59%

3-(hepta-1,6-diyn-1-yl)-3-hydroxyindolin-2-one (3.71). A flame dried 200 mL round bottomed flask under a nitrogen atmosphere was charged with 1,6-heptadiyne (**3.70**) (526 mg, 5.71 mmol) and tetrahydrofuran (57 mL). To this solution at room temperature was added ethylmagnesium bromide (1.7 mL of a 3 M solution in Et_2O, 5.10 mmol). After 45 min of stirring, isatin (**3.51**) was added as a solution in tetrahydrofuran (5.8 mL). The reaction was left to stir for 1 h, at which time all starting material had been consumed based on TLC. The reaction was quenched by adding saturated aqueous ammonium chloride (15 mL) and water (15 mL). The aqueous phase was extracted with ethyl acetate (3 x 15 mL). The combined organic layers were washed with brine (20 mL), dried over magnesium sulfate, and concentrated. The crude material was purified by silica gel flash column chromatography eluting with 40% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide propargyl alcohol **3.71** in a 59% yield.

Data for **3.71**: (JMO5-84)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 9.13 (s, 1H), 7.50 (d, *J* = 7.0 Hz, 1H), 7.27 (t, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.95 (d, *J* = 7.7 Hz, 1H), 4.60 (s, 1H), 2.31 (t, *J* = 7.0 Hz, 2H), 2.22 (td, *J* = 7.7, 2.8 Hz, 2H), 1.89 (s, 1H), 1.66 (quin, *J* = 7.0 Hz, 2H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 177.3, 140.2, 130.4, 130.0, 124.8, 123.8, 111.0, 87.0, 83.3, 69.7, 69.1, 27.0, 17.9, 17.5

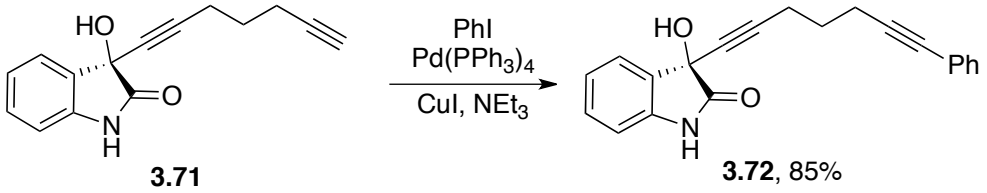
MS *m/z* (%)

240 (100), 222 (40), 212 (10), 194 (10), 184 (10), 174 (10), 132 (10)

HRMS TOF MS ES+ $C_{15}H_{14}NO_2$

Calculated: 240.1025; Found: 240.1057

TLC R_f = 0.36 (50% ethyl acetate/hexanes) [Silica gel, UV, p-anisaldehyde]



3.71 **3.72**, 85%

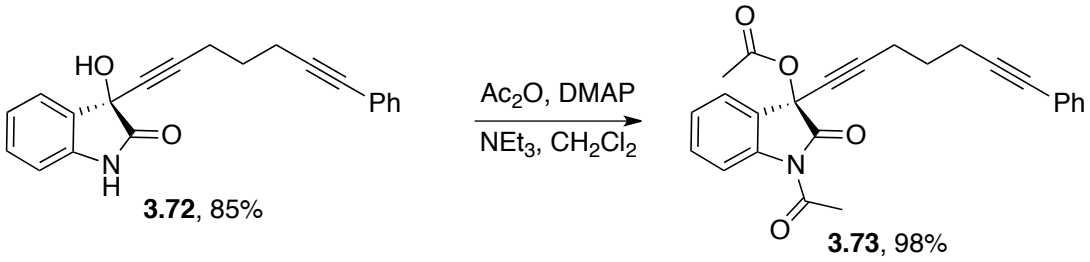
3-hydroxy-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-2-one (3.72). A 10 mL round bottomed flask under an argon atmosphere was charged with alkyne **3.71** (239 mg, 1.0 mmol), tetrahydrofuran (0.5 mL), iodobenzene (0.224 mL, 2.0 mmol), and triethylamine (2.9 mL, 21.0 mmol). To this solution at room temperature was added tetrakis(triphenylphosphine)palladium (0) (11.6 mg, 0.01 mmol) followed by copper (I) iodide (3.8 mg, 0.02 mmol). The reaction was left to stir at room temperature overnight. The reaction mixture was filtered through a plug of Celite and concentrated. The crude material was purified by silica gel flash column chromatography eluting with 50% ethyl acetate/hexanes to provide propargyl alcohol **3.72** as an orange solid in 85% yield.

Data for **3.72**: (JMO5-114)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.97 (s, 1H), 7.52 (ddt, *J* = 7.5, 1.2, 0.6 Hz, 1H), 7.40-7.32 (m, 2H), 7.31-7.25 (m, 4H), 7.12 (td, *J* = 7.6, 1.0 Hz, 1H), 6.92-6.86 (m, 1H), 3.55 (d, *J* = 0.6 Hz, 1H), 2.47 (t, *J* = 9 Hz, 2H), 2.41 (t, *J* = 6 Hz, 2H), 1.79 (quin, *J* = 7.0 Hz, 2H)

TLC R_f = 0.19 (50% EtOAc/hexanes) [silica gel, UV]



3.72, 85% **3.73**, 98%

1-acetyl-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-3-yl acetate (3.73). A 10 mL vial was charged with the propargyl alcohol **3.72** (268 mg, 0.851 mmol) and dichloromethane (2.7 mL). To this solution was added 4-dimethylaminopyridine (10.4 mg, 0.085 mmol), triethylamine (0.425 mL, 3.06 mmol) and acetic anhydride (0.193 mL, 2.04 mmol). The reaction was left to stir at room temperature for 1 h at which time all starting material had been consumed based on TLC analysis. The reaction was quenched by addition of saturated aqueous sodium bicarbonate (3 mL). The aqueous phase was extracted with dichloromethane (3 x 3 mL). The combined organic phases were dried over magnesium sulfate and concentrated. The crude material was purified using a silica plug, eluting with 150 mL of 50% ethyl acetate/hexanes. The solution was concentrated to provide 332 mg of an amber colored oil in 98% yield.

Data for **3.73**: (JMO5-116)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 8.25 (d, *J* = 8.1 Hz, 1H), 7.48-7.39 (m, 2H), 7.39-7.33 (m, 2H), 7.30-7.26 (m, 3H), 7.26-7.21 (m, 1H), 2.70 (s, 3H), 2.47 (t, *J* = 7.2 Hz, 2H), 2.45 (t, *J* = 7.2 Hz, 2H), 2.11 (s, 3H), 1.82 (quin, *J* = 7.1 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 171.0, 170.6, 169.0, 139.9, 131.6 (2C), 130.8, 128.3 (2C), 127.8, 126.5, 125.9, 123.6, 123.0, 117.0, 90.4, 88.6, 81.5, 73.9, 73.3, 27.2, 26.5, 20.5, 18.6, 18.2

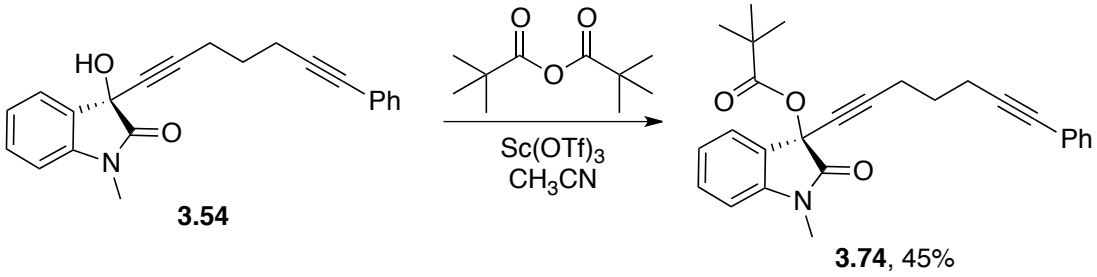
MS *m/z* (%)

422 (50), 379 (25), 362 (25), 336 (30), 298 (100)

HRMS TOF MS ES+ $C_{25}H_{21}NO_4Na$

Calculated: 422.1368; Found: 422.1345

TLC R_f = 0.74 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-methyl-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-3-yl pivalate (3.74). A flame dried 5 mL round bottomed flask under a nitrogen atmosphere was charged with the propargyl alcohol **3.54** (134 mg, 0.407 mmol) and acetonitrile (1.6 mL). Scandium triflate (4.0 mg, 0.008 mmol) was added followed by trimethylacetic anhydride (0.124 mL, 0.611 mmol). The reaction was left to stir at room temperature overnight at which time substantial starting material still remained based on TLC. Additional trimethylacetic anhydride (75 mg) and Scandium triflate (20 mg) were added and the reaction was heated to 40 °C for 4 h. At this time, the reaction was no longer

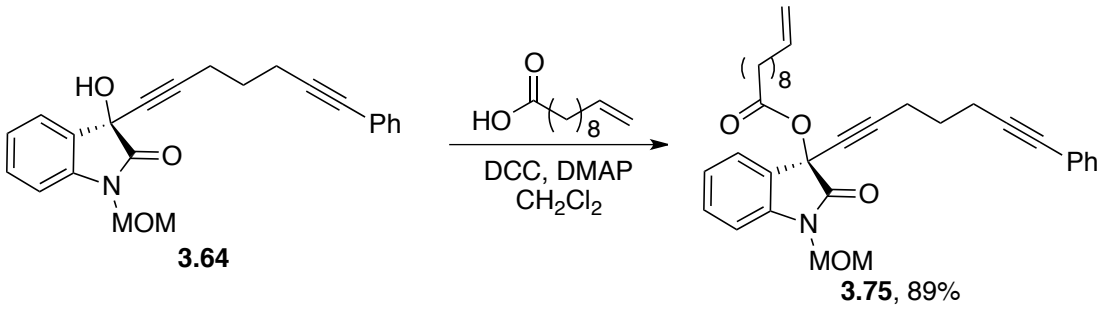
progressing based on TLC. The reaction was quenched by adding saturated aqueous sodium bicarbonate solution (2 mL), water (2 mL), and ether (4 mL). The aqueous layer was extracted with ether (3 x 4 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and concentrated. The crude material was purified by silica gel flash chromatography eluting with 24% ethyl acetate/hexanes to provide propargyl pivalate **3.74** in 45% yield.

Data for **3.74**: (JMO6-4)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.38-7.32 (m, 4H), 7.29-7.25 (m, 3H), 7.07 (dt, J = 0.8, 7.6 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 3.26 (s, 3H), 2.46 (t, J = 6.8 Hz, 2H), 2.42 (t, J = 7.2 Hz, 2H), 1.81 (quin, J = 6.8 Hz, 2H), 1.21 (s, 9H)

TLC R_f = 0.72 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



1-(methoxymethyl)-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-3-yl undec-10-enoate (3.75). A two-dram vial was charged with propargyl alcohol **3.64** (111 mg, 0.309 mmol) and dichloromethane (1 mL). 10-Undecenoic acid (65 μL, 0.309 mmol) was added by syringe and the reaction mixture was cooled to 0 °C with stirring. 4-Dimethylaminopyridine (3.8 mg, 0.0309 mmol) was added followed by *N,N*-dicyclohexylcarbodiimide (70 mg, 0.340 mmol). The reaction was then warmed to rt and left to stir overnight at which time all starting material had

been consumed based on TLC. The reaction mixture was diluted with dichloromethane (10 mL) and washed with 0.1 M aqueous hydrochloric acid (2 x 10 mL). The organic layer was then washed with water (2 x 10 mL) and brine (10), dried over magnesium sulfate, and concentrated. The crude material was purified by silica gel flash chromatography eluting with 10% ethyl acetate/hexanes to provide ester **3.75** in 89% yield.

Data for **3.75**: (JMO9-140)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.42 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.40 -7.34 (m, 3H), 7.31-7.27 (m, 3H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 7.9 Hz, 1H), 5.82 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.21 (d, *J* = 11.1 Hz, 1H), 5.17 (d, *J* = 11.1 Hz, 1H), 5.06-4.99 (m, 1H), 4.99-4.92 (m, 1H), 3.44 (s, 3H), 2.48 (t, *J* = 7.0 Hz, 2H), 2.45 (t, *J* = 7.0 Hz, 2H), 2.39 (td, *J* = 7.6, 4.1 Hz, 2H), 2.09-2.00 (m, 2H), 1.82 (p, *J* = 7.1 Hz, 2H), 1.63-1.54 (m, 2H), 1.42-1.33 (m, 2H), 1.31-1.25 (m, 8H)

^{13}C NMR (125 MHz, $CDCl_3$)

δ 171.51, 171.48, 141.7, 139.2, 131.5 (2C), 130.4, 128.2 (2C), 127.7, 126.9, 123.73, 123.67, 123.2, 114.2, 110.3, 88.7, 81.4, 74.4, 73.3, 72.1, 68.0, 66.0, 33.8, 29.2, 29.1, 29.0, 28.88, 28.86, 27.3, 24.7, 18.6, 18.2

IR (thin film)

2928, 2854, 1745, 1613 cm^{-1}

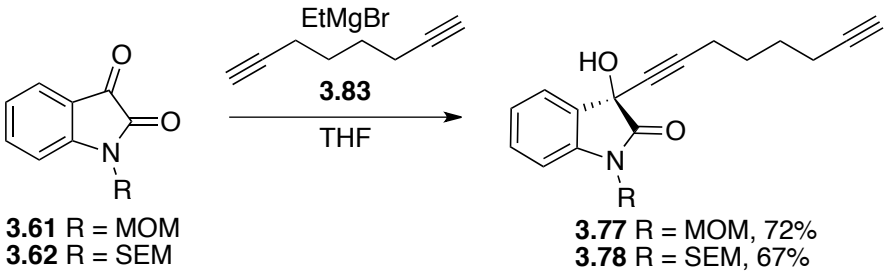
MS *m/z* (%)

548 (20), 381 (50), 380 (35), 336 (20), 310 (100)

HRMS TOF MS ES+ $C_{34}H_{39}NO_4Na$

Calculated: 548.2777; Found: 548.2802

TLC R_f = 0.66 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.61 R = MOM
3.62 R = SEM

3.77 R = MOM, 72%
3.78 R = SEM, 67%

General Procedure 3

3-hydroxy-1-(methoxymethyl)-3-(octa-1,7-diyn-1-yl)indolin-2-one (3.77). A flame dried 50 mL round bottomed flask under a nitrogen atmosphere was charged with 1,7-octadiyne (**3.83**) (206 mg, 1.94 mmol) and tetrahydrofuran (19 mL). To this solution at room temperature was added ethyl magnesium bromide (0.52 mL of a 3.0 M solution in ether, 1.57 mmol). The reaction was stirred for 1 h at which time *N*-MOM isatin **3.61** (200 mg, 1.05 mmol) was added as a solution in tetrahydrofuran (3 mL). After 2.5 h, all starting material had been consumed based on TLC. Saturated aqueous ammonium chloride solution (10 mL) and water (5 mL) were added to quench the reaction. The layers were separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over magnesium sulfate, and concentrated. The residue was purified by silica gel flash chromatography eluting with 20% ethyl acetate/hexanes to provide 226 mg of the title compound **3.77** in 72% yield as a yellow oil.

Data for **3.77**: (JMO5-30)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.53 (d, *J* = 7.5 Hz, 1H), 7.36 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.17 (dt, *J* = 0.6, 7.5 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 5.10 (d, *J* = 10.8 Hz, 1H),

3.35 (s, 3H), 2.26 (t, J = 6.9 Hz, 2H), 2.19 (dt, J = 2.7, 6.9 Hz, 2H), 1.93 (t, J = 2.4 Hz, 1H), 1.68 – 1.53 (m, 4H)

IR (thin film)

3368, 3291, 2940, 2234, 1738, 1614 cm^{-1}

HRMS TOF MS ES+ $C_{18}H_{19}NO_3Na$

Calculated: 320.1263; Found: 320.1234

TLC R_f = 0.67 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

3-hydroxy-3-(octa-1,7-diyn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-2-one (3.78). Following General Procedure 3: To a solution of 1,7-octadiyne (1.0 mL, 7.73 mmol) in tetrahydrofuran (77 mL) was added ethylmagnesium bromide (2.12 mL of a 3.0 M solution in Et_2O, 6.37 mmol). After 1 h, SEM-isatin **3.62** (1.26 g, 4.55 mmol) was added as a solution in tetrahydrofuran (15 mL). The reaction was left to stir for 2 h, at which time it was complete by TLC. The crude material was purified by silica gel flash chromatography eluting with 10-25% ethyl acetate/hexanes to provide 1.16 g of **3.78** in a 67% yield.

Data for **3.78**: (JMO9-142)

^{1}H NMR (300 MHz, $CDCl_3$)

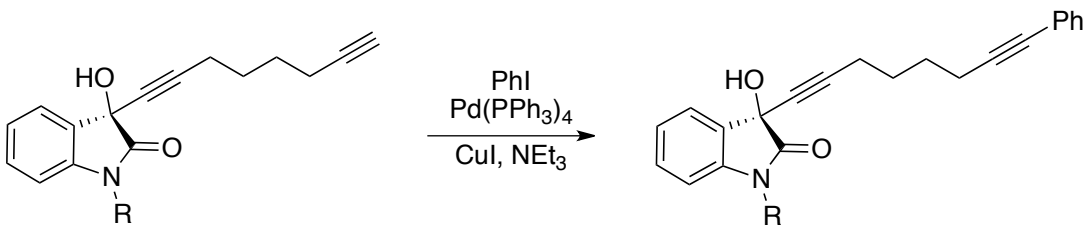
δ 7.57 (d, J = 7.4 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 5.21 (d, J = 11.1 Hz, 1H), 5.16 (d, J = 11.1 Hz, 1H), 3.62 (t, J = 8.2 Hz, 2H), 3.26 (s, 1H), 2.29 (t, J = 6.5 Hz, 2H), 2.25-2.20 (m, 2H), 1.98-1.96 (m, 1H), 1.67-1.63 (m, 4H), 0.95 (t, J = 8.2 Hz, 2H), 0.00 (s, 9H)

IR 3298, 2950, 2234, 1737, 1615 cm^{-1}

HRMS TOF MS ES+ $C_{22}H_{29}NO_3NaSi$

Calculated: 406.1814; Found: 406.1834

TLC R_f = 0.41 (50% EtOAc/hexanes) [silica gel, UV]



3.77 R = MOM
3.78 R = SEM

3.79 R = MOM, 66%
3.80 R = SEM, 71%

General Procedure 4

3-hydroxy-1-(methoxymethyl)-3-(8-phenylocta-1,7-diyn-1-yl)indolin-2-one (3.79). A 10 mL round bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **3.77** (211 mg, 0.710 mmol), tetrahydrofuran (0.3 mL), and triethylamine (2.1 mL, 14.9 mmol). Iodobenzene (290 mg, 1.42 mmol) was added followed by copper (I) iodide (2.7 mg, 0.0142 mmol) and finally tetrakis(triphenylphosphine)palladium(0) (8.2 mg, 7.1×10^{-3} mmol). The reaction was left to stir at rt overnight. The reaction mixture was diluted with ether (5 mL), filtered through a plug of Celite, and concentrated. The residue was purified by silica gel flash chromatography eluting with 25% ethyl acetate/hexanes to afford 174 mg of the title compound **3.79** in 66% yield as a light amber oil.

Data for **3.79**: (JMO5-34)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.54 (d, J = 7.5 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.29 – 7.25 (m, 3H), 7.15 (t, J = 7.5 Hz, 1H), 7.04 (d, J = 8.1 Hz, 1H), 5.14 (d, J = 11.1 Hz, 1H), 5.10 (d, J = 11.1 Hz, 1H), 3.34 (s, 3H), 3.13 (s, 1H), 2.41 (t, J = 6.6 Hz, 2H), 2.30 (t, J = 6.9 Hz, 2H), 1.72 – 1.65 (m, 4H)

TLC R_f = 0.29 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

3-hydroxy-3-(8-phenylocta-1,7-diyn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-2-one (3.80). Following General Procedure 4: A 10 mL round bottomed flask under a nitrogen atmosphere was charged with alkyne **3.78** (582 mg, 1.56 mmol), iodobenzene (340 μL, 3.03 mmol) and triethylamine (4.4 mL, 31.8 mmol). To the stirred solution at rt was added tetrakis(triphenylphosphine)palladium (0) (17.5 mg, 0.015 mmol) followed by copper (I) iodide (6.1 mg, 0.032 mmol). The crude product was purified by silica gel flash chromatography eluting with 20-22% ethyl acetate/hexanes to provide 495 mg of **3.80** in a 71% yield.

Data for **3.80**: (JMO9-160)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.57 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.41-7.39 (m, 2H), 7.36 (td, *J* = 7.8, 1.2 Hz, 1H), 7.30-7.27 (m, 3H), 7.16 (td, *J* = 7.6, 0.9 Hz, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 5.20 (d, *J* = 11.1 Hz, 1H), 5.14 (d, *J* = 11.1 Hz, 1H), 3.71 (s, 1H), 3.61 (t, *J* = 8.2 Hz, 2H), 2.42 (t, *J* = 6.4 Hz, 2H), 2.30 (t, *J* = 6.5 Hz, 2H), 1.70 (dd, *J* = 6.2, 3.2 Hz, 4H), 0.95-0.92 (m, 2H), -0.02 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$)

δ 174.6, 141.3, 131.5, 130.3, 128.8, 128.1, 127.5, 124.5, 123.92, 123.79, 110.3, 89.5, 87.7, 80.9, 77.2, 69.7, 69.4, 66.1, 27.7, 27.2, 18.8, 18.4, 17.6, -1.5

IR (thin film)

3381, 2949, 2234, 1738, 1615 cm^{-1}

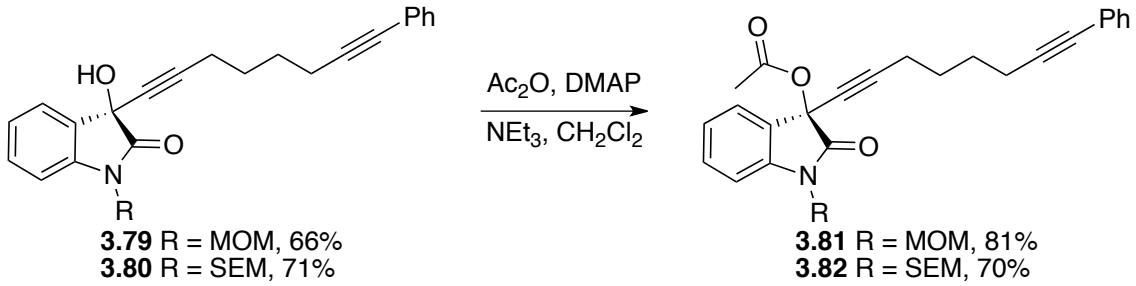
MS *m/z* (%)

482 (20), 263 (10), 220 (15), 219 (100)

HRMS TOF MS ES+ $C_{28}H_{33}NO_3NaSi$

Calculated: 482.2127; Found: 482.2153

TLC R_f = 0.16 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.79 R = MOM, 66%
3.80 R = SEM, 71%

3.81 R = MOM, 81%
3.82 R = SEM, 70%

1-(methoxymethyl)-2-oxo-3-(8-phenylocta-1,7-diyn-1-yl)indolin-3-yl acetate (3.81). Following General Procedure 2: To a solution of propargyl alcohol **3.79** (174 mg, 0.466 mmol) in dichloromethane (1.5 mL) was added 4-dimethylaminopyridine (5.7 mg, 0.047 mmol), triethylamine (234 μL, 1.68 mmol), and acetic anhydride (105 μL, 1.11 mmol). The reaction mixture was left to stir overnight at rt. The residue was purified by silica gel flash chromatography eluting with 30% ethyl acetate/hexanes to afford 157 mg of propargyl acetate **3.81** in 81% yield as a lightly colored oil.

Data for **3.81**: (JMO5-58)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.43 – 7.31 (m, 4H), 7.30 – 7.25 (m, 3H), 7.10 (dt, *J* = 1.2, 7.8 Hz, 1H), 7.06 (d, *J* = 7.8 Hz, 1H), 5.19 (d, *J* = 11.1 Hz, 1H), 5.13 (d, *J* = 11.1 Hz, 1H), 3.40 (s, 3H), 2.39 (t, *J* = 6.9 Hz, 2H), 2.30 (t, *J* = 6.9 Hz, 2H), 2.10 (s, 3H), 1.74 – 1.60 (m, 4H)

^{13}C NMR δ 171.3, 168.5, 141.6, 131.5, 130.3, 128.3, 128.1, 127.5, 126.8, 123.8, 123.7, 123.2, 110.2, 89.5, 89.4, 80.9, 73.9, 72.0, 56.4, 27.7, 27.1, 20.6, 18.8, 18.5

IR (thin film)

2938, 2243, 1746, 1613 cm^{-1}

MS *m/z* (%)

438 (20), 394 (10), 324 (100), 296 (30), 294 (15), 282 (15)

HRMS TOF MS ES+ $C_{26}H_{25}NO_4Na$

Calculated: 438.1681; Found: 438.1670

TLC R_f = 0.18 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

2-oxo-3-(8-phenylocta-1,7-diyn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-3-yl acetate (3.82). Following General Procedure 2: To a solution of propargyl alcohol **3.80** (478 mg, 1.04 mmol) in dichloromethane (3.5 mL) was added 4-dimethylaminopyridine (12.7 mg, 0.104 mmol), triethylamine (0.520 mL, 3.74 mmol), and acetic anhydride (0.236 mL, 2.49 mmol). All starting material had been consumed within 2 h. The crude material was purified via silica gel flash chromatography eluting with 11% ethyl acetate/hexanes to provide 364 mg of the title compound **3.82** in a 70% yield.

Data for **3.82**: (JMO9-162)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.44-7.39 (m, 2H), 7.36 (td, *J* = 7.8, 1.3 Hz, 1H), 7.30-7.28 (m, 3H), 7.13-7.09 (m, 2H), 5.24 (d, *J* = 11.2 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 3.76-3.71 (m, 1H), 3.63 (td, *J* = 9.9, 6.6 Hz, 1H), 2.42 (t, *J* = 6.6 Hz, 2H), 2.33-2.30 (m, 2H), 2.10 (s, 3H), 1.74-1.64 (m, 4H), 1.01-0.91 (m, 2H), -0.01 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$)

δ 171.2, 168.4, 141.9, 131.5 (2C), 130.3, 128.2 (2C), 127.5, 126.8, 123.8, 123.6, 123.3, 110.3, 89.5, 89.3, 80.9, 73.9, 73.5, 69.9, 66.0, 27.7, 27.1, 20.6, 18.9, 18.6, 17.7, -1.5 (3C)

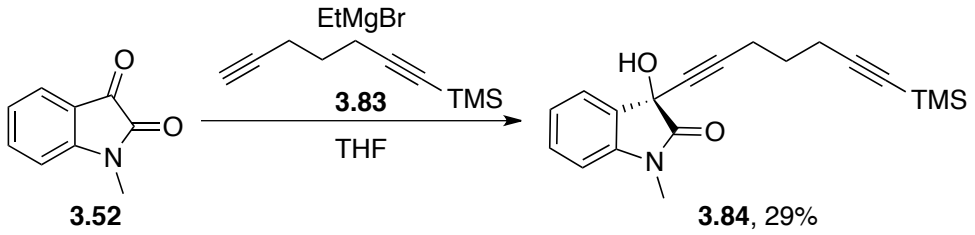
IR (thin film)

2949, 2243, 1747, 1614 cm^{-1}

HRMS TOF MS ES+ $C_{30}H_{35}NO_4NaSi$

Calculated: 524.2233; Found: 524.2211

TLC R_f = 0.39 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.52 **3.84**, 29%

3-hydroxy-1-methyl-3-(7-(trimethylsilyl)hepta-1,6-diyn-1-yl)indolin-2-one (3.84). A flame-dried 10 mL round bottomed flask under a nitrogen atmosphere was charged with diyne **3.83** (106 mg, 0.645 mmol) and tetrahydrofuran (3.2 mL) and cooled to -78 °C. To this solution was added *n*-butyllithium (0.40 mL of a 1.6 M hexanes solution, 0.645 mmol) dropwise over a period of 5 min. The reaction was maintained at -78 °C for 1 h at which time *N*-methylisatin (**3.52**) (95 mg, 0.586 mmol) in tetrahydrofuran (1.5 mL) was added dropwise over a period of 5 min. The reaction was maintained at -78 °C for 30 min and was then allowed to warm to rt and stir overnight at which time all starting material had been consumed based on TLC. The reaction was diluted with ether (5 mL) and poured into a separatory funnel containing ether (10 mL) and saturated aqueous ammonium chloride solution (10 mL). The aqueous phase was separated and extracted with ether (3 x 5 mL). The combined organic layers were washed with brine (10 mL),

dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography eluting with 25% ethyl acetate/hexanes to afford 55 mg of propargyl alcohol **3.84** in 29% yield as a white solid. Additionally, 30 mg of the desilylated propargyl alcohol was isolated.

Data for **3.84**: (JMO3-96)

Mp 124 – 126 °C

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.52 (dt, *J* = 7.5, 0.3 Hz, 1H), 7.34 (dt, *J* = 0.9, 7.8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.20 (s, 3H), 2.31 (t, *J* = 7.2 Hz, 2H), 2.26 (t, *J* = 6.9 Hz, 2H), 1.69 (p, *J* = 7.2 Hz, 2H), 0.122 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 174.3, 142.9, 130.3, 129.2, 124.4, 123.7, 108.7, 106.0, 86.8, 85.2, 77.4, 69.1, 27.2, 26.5, 19.0, 18.0, 0.06 (3C)

IR (thin film)

3357, 2957, 2236, 2173, 1713, 1614 cm^{-1}

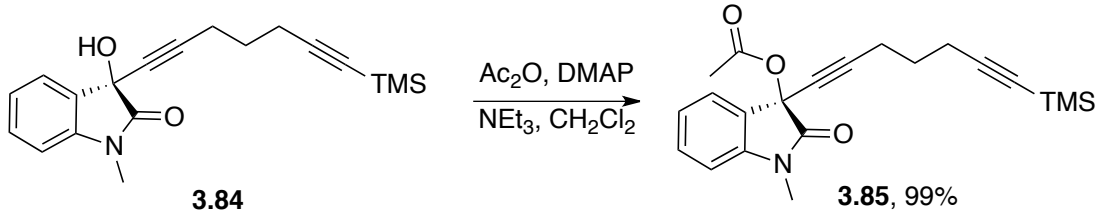
MS EI+

m/z (%) 325 (35), 310 (38), 252 (90), 224 (30), 115 (31), 109 (100), 96 (59), 81 (44), 75 (48), 73 (87)

HRMS EI-HRMS: $C_{19}H_{23}NO_2Si$

Calculated 325.1498; Found 325.1489

TLC R_f = 0.48 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.84 **3.85**, 99%

1-methyl-2-oxo-3-(7-(trimethylsilyl)hepta-1,6-diyn-1-yl)indolin-3-yl acetate (3.85). A flame-dried 5 mL round bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **3.84** (55 mg, 0.169 mmol) and dichloromethane (0.53 mL). 4-Dimethylaminopyridine (2.1 mg, 0.0169 mmol) was added followed by triethylamine (85 μL, 0.609 mmol) and finally acetic anhydride (38 μL, 0.408 mmol). The reaction was allowed to stir at room temperature for 30 min at which time complete consumption of the starting material was observed by TLC. The reaction was then diluted with dichloromethane (3 mL) and saturated aqueous sodium bicarbonate solution (2 mL) was added to quench the reaction. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were washed with brine (5 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by silica gel flash chromatography eluting with 20% ethyl acetate/hexanes to provide 62 mg of propargyl acetate **3.85** in 99% yield as a colorless oil.

Data for **3.85**: (JMO3-101)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.42 (d, *J* = 7.0 Hz, 1H), 7.35 (dt, 1.2, 7.8 Hz, 1H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 3.26 (s, 3H), 2.35 (t, *J* = 7.5 Hz, 2H), 2.27 (t, *J* = 7.2 Hz, 2H), 2.08 (s, 3H), 1.71 (p, *J* = 7.2 Hz, 2H), 0.128 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 170.8, 168.5, 143.5, 130.4, 127.0, 123.5, 123.2, 108.7, 105.9, 88.5, 85.3, 74.0, 73.2, 27.1, 26.8, 20.7, 19.0, 18.1, 0.05 (3C)

IR (thin film)

2958, 2901, 2245, 2173, 1741, 1614 cm^{-1}

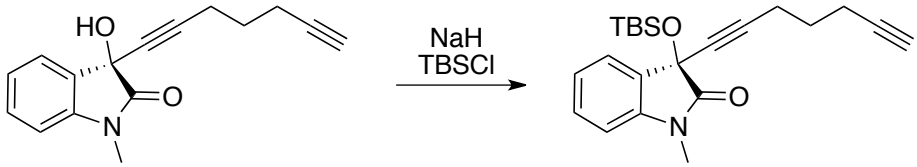
MS EI+

m/z (%) 398 (27), 397 (100), 396 (91), 379 (50), 378 (95), 368 (72)

HRMS TOF MS ES+: $C_{21}H_{25}NO_3NaSi$

Calculated: 390.1502 Found: 390.1538

TLC R_f = 0.25 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.86 **3.87**, 88%

3-((*tert*-butyldimethylsilyl)oxy)-3-(hepta-1,6-diyn-1-yl)-1-methylindolin-2-one (3.87). A flame dried 50 mL round bottomed flask under a nitrogen atmosphere was charged with propargyl alcohol **3.86** (628 mg, 2.48 mmol) and tetrahydrofuran (10 mL) and cooled to 0 °C. Sodium hydride (109.2 mg, 2.73 mmol, 60% dispersion in mineral oil) was added in one portion and the reaction was left to stir at 0 °C for 15 min. Chlorotrimethylsilane (411 mg, 2.73 mmol) was then added as a solution in tetrahydrofuran (5 mL). The reaction was allowed to warm to rt and left to stir overnight at which time the reaction had not reached completion based on TLC analysis. The reaction mixture was heated to 55 °C for an additional 12 h, until complete based on TLC analysis. The reaction was cooled to rt and quenched by adding water (30 mL) and ether (30 mL). The aqueous layer was extracted with ether (3 x 15 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude oil was

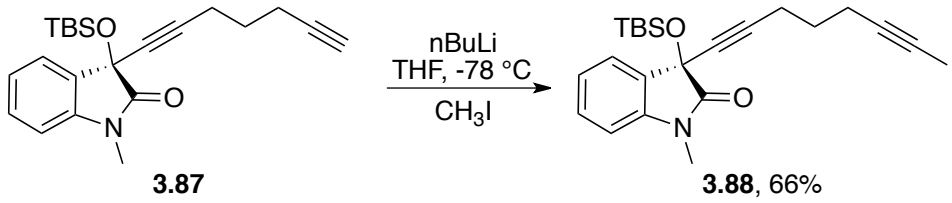
purified by silica gel flash chromatography eluting with 10% ethyl acetate/hexanes to provide 798 mg of **3.87** in an 88% yield as a yellow oil.

Data for **3.87**: (JMO5-174)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.39 (ddd, *J* = 7.4, 1.3, 0.5 Hz, 1H), 7.31 (td, *J* = 7.7, 1.3 Hz, 1H), 7.09 (td, *J* = 7.5, 1.0 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 3.18 (s, 3H), 2.36-2.31 (m, 2H), 2.25 (td, *J* = 7.0, 2.6 Hz, 2H), 1.93 (t, *J* = 2.7 Hz, 1H), 1.76-1.66 (m, 2H), 0.88 (s, 9H), 0.29 (s, 3H), 0.17 (s, 3H)

TLC R_f = 0.67 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.87 **3.88**, 66%

3-((*tert*-butyldimethylsilyl)oxy)-1-methyl-3-(octa-1,6-diyn-1-yl)indolin-2-one (3.88). A flame dried 10 mL pear shaped flask was charged with alkyne **3.87** (113 mg, 0.308 mmol). The alkyne was then azeotroped with freshly distilled benzene (3 x 0.5 mL) to remove any trace water. The flask was evacuated and backfilled with nitrogen two times and maintained under a nitrogen atmosphere for the remainder of the reaction. Tetrahydrofuran (3.1 mL) was added to the reaction flask and the solution was cooled to -78 °C. To the cold solution was added *n*-butyllithium (0.212 mL of a 1.6 M solution in hexanes, 0.339 mmol) dropwise. The reaction was then allowed to warm for 5 min and was subsequently cooled back to -78 °C at which time iodomethane (96 μL, 1.54 mmol) was added dropwise. The reaction was allowed to warm to rt over the course of 2 h and then left to stir at rt overnight. The reaction was diluted with ether (2

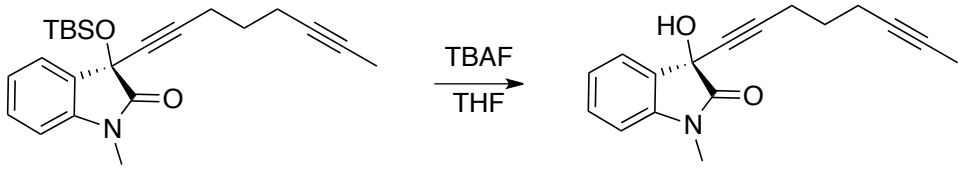
mL) and quenched by adding saturated aqueous ammonium chloride (2 mL). The aqueous layer was extracted with ether (3 x 2 mL). The combined organic layers were washed with brine (4 mL), dried over magnesium sulfate, and concentrated to provide 77 mg of the title compound **3.88** in a 66% yield. Based on the purity by ^{1}H NMR, purification of **3.88** was not necessary.

Data for **3.88**: (JMO5-180)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.39 (dd, J = 7.4, 0.5 Hz, 1H), 7.31 (td, J = 7.8, 0.8 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 6.79 (d, J = 7.9 Hz, 1H), 3.18 (s, 3H), 2.30 (t, J = 7.7 Hz, 2H), 2.21-2.14 (m, 2H), 1.75 (t, J = 2.5 Hz, 3H), 1.65 (quintet, J = 7.1 Hz, 2H), 0.88 (s, 9H), 0.29 (s, 3H), 0.17 (s, 3H)

TLC R_f = 0.67 (two elutions of 20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.88 **3.89**, 97%

3-hydroxy-1-methyl-3-(octa-1,6-diyn-1-yl)indolin-2-one (3.89). In a two-dram vial, the TBS ether **3.88** (77 mg, 0.202 mmol) was dissolved in tetrahydrofuran (2 mL). Tetrabutylammonium fluoride (0.303 mL of a 1 M solution in THF, 0.303 mmol) was added dropwise. During addition, the solution became dark in color. After 15 min, all starting material had been consumed based on TLC analysis. The reaction mixture was concentrated then applied to a silica gel flash column. The column was eluted with 40% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide 52.2 mg of **3.89** in a 97% yield.

Data for **3.89**: (JMO5-188)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.51 (d, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.59 (s, 1H), 3.21 (s, 3H), 2.32 (t, *J* = 7.2 Hz, 2H), 2.21-2.14 (m, 2H), 1.74 (t, *J* = 2.7 Hz, 3H), 1.65 (quin, *J* = 7.2 Hz, 2H)

TLC R_f = 0.36 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

3.89 **3.90**, 79%

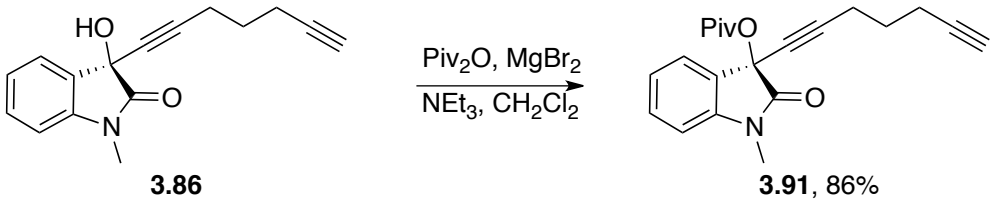
1-methyl-3-(octa-1,6-diyn-1-yl)-2-oxoindolin-3-yl acetate (3.90). A two-dram vial under a nitrogen atmosphere was charged with propargyl alcohol **3.89** (52 mg, 0.195 mmol) and dichloromethane (0.65 mL). To this solution was added 4-dimethylaminopyridine (2.4 mg, 0.0195 mmol), triethylamine (97 μL, 0.701 mmol), and acetic anhydride (44 μL, 0.467 mmol). Within 15 min, all starting material had been consumed based on TLC analysis. The reaction was diluted with dichloromethane (1 mL) and saturated aqueous sodium bicarbonate solution (1 mL) was added. The aqueous layer was extracted with dichloromethane (2 x 1 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The crude material was purified by silica gel flash chromatography eluting with 30% ethyl acetate/hexanes to provide 47.4 mg of **3.90** in a 79% yield.

Data for **3.90**: (JMO5-190)

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.41 (dd, *J* = 7.4, 1.3 Hz, 1H), 7.34 (td, *J* = 7.8, 1.3 Hz, 1H), 7.08 (td, *J* = 7.6, 1.0 Hz, 1H), 6.85-6.83 (m, 1H), 3.25 (s, 3H), 2.33 (t, *J* = 7.0 Hz, 2H), 2.19-2.14 (m, 2H), 2.07 (s, 3H), 1.74 (t, *J* = 2.5 Hz, 3H), 1.66 (quin, *J* = 7.2 Hz, 2H)

TLC R_f = 0.63 (50% EtOAc/hexanes) [silica gel, UV]



3.86 **3.91**, 86%

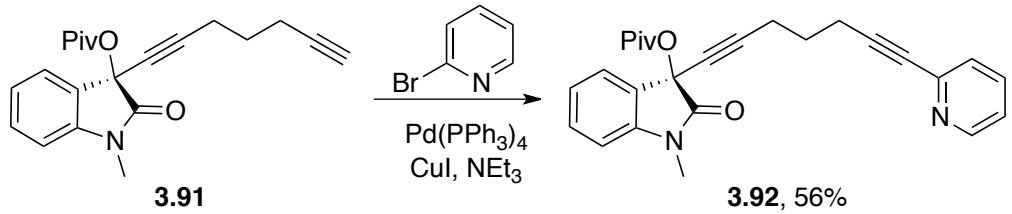
3-(hepta-1,6-diyn-1-yl)-1-methyl-2-oxoindolin-3-yl pivalate (3.91). A 10 mL round bottomed flask was charged with magnesium bromide (2.93 mL of a 0.27 M solution in THF, 0.791 mmol). The solution was evaporated under a stream of nitrogen and the resulting solid was taken back up in dichloromethane (3.6 mL). The magnesium bromide solution was then cannulated into a second flask containing trimethylacetic anhydride (161 μL, 0.791 mmol). Triethylamine (165 μL, 1.19 mmol) was added followed by propargyl alcohol **3.86** (100 mg, 0.395 mmol). The solution was left to stir at rt overnight. Water (5 mL) was added to quench the reaction. The layers were separated and the aqueous layer was extracted with dichloromethane (5 mL). The combined organic layers were concentrated and the residue was purified by silica gel flash chromatography eluting with 25% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide 115 mg of propargyl pivalate **3.91** in 86% yield.

Data for **3.91**: (JMO8-198)

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.38-7.34 (m, 2H), 7.11-7.07 (m, 1H), 6.86 (dd, *J* = 8.3, 0.8 Hz, 1H), 3.28 (s, 3H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.26 (td, *J* = 7.0, 2.6 Hz, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.75 (quintet, *J* = 7.1 Hz, 2H), 1.23 (s, 9H)

TLC R_f = 0.69 (50% EtOAc/hexanes) [silica gel, UV]



3.91 **3.92**, 56%

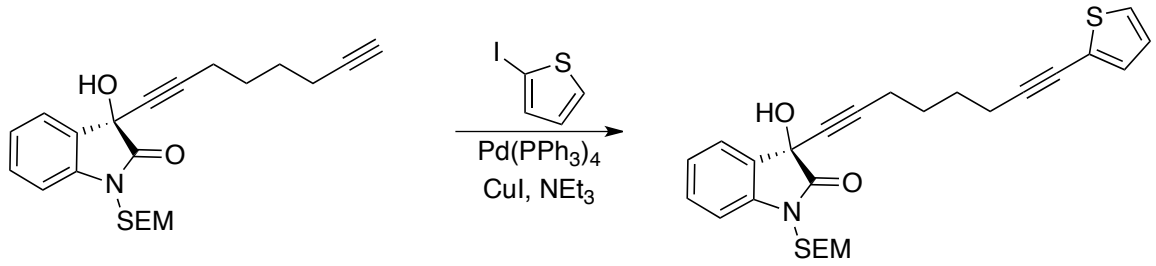
1-methyl-2-oxo-3-(7-(pyridin-2-yl)hepta-1,6-diyn-1-yl)indolin-3-yl pivalate (3.92). A 5 mL round bottomed flask under an argon atmosphere was charged with alkyne **3.91** (145 mg, 0.430 mmol), tetrahydrofuran (0.22 mL), triethylamine (1.26 mL, 9.04 mmol), and 2-bromopyridine (136 mg, 0.861 mmol). To this solution was added tetrakis(triphenylphosphine)palladium(0) (5.0 mg, 4.3 x 10^{-3} mmol) and copper (I) iodide (1.6 mg, 8.6 x 10^{-3} mmol) with stirring. The reaction was left to stir at rt overnight at which time it was diluted with ether (3 mL) and filtered through a plug of Celite. The crude material was purified by silica gel flash column chromatography eluting with 35% ethyl acetate/hexanes to provide 100 mg of the title compound **3.92** in a 56% yield.

Data for **3.92**: (JMO9-132)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 8.52 (t, *J* = 1.3 Hz, 1H), 7.60 (td, *J* = 7.7, 1.7 Hz, 1H), 7.35-7.30 (m, 3H), 7.18 (dd, *J* = 7.1, 5.1 Hz, 1H), 7.06 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 3.25 (s, 3H), 2.49 (t, *J* = 7.1 Hz, 2H), 2.41 (t, *J* = 7.0 Hz, 2H), 1.82 (quintet, *J* = 7.1 Hz, 2H), 1.20 (s, 9H).

TLC $R_f = 0.22$ (35% ethyl acetate/hexanes) [silica gel, UV, p-anisaldehyde]



3.78 **3.93**, 70%

3-hydroxy-3-(8-(thiophen-2-yl)octa-1,7-diyn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl) indolin 2-one (3.93). A 5 mL round bottomed flask was charged with alkyne **3.78** (83 mg, 0.216 mmol), tetrahydrofuran (0.2 mL), triethylamine (0.631 mL, 4.54 mmol), and 2-iodothiophene (48 μL, 0.432 mmol). To this solution was added tetrakis(triphenylphosphine)palladium(0) (2.5 mg, 2.16 x 10^{-3} mmol) and copper (I) iodide (0.82 mg, 4.32 x 10^{-3} mmol). The reaction was left to stir at rt under a nitrogen atmosphere overnight. The reaction mixture was diluted in ether and filtered through a plug of Celite. The crude material was purified by silica gel flash chromatography eluting with 20% ethyl acetate/hexanes to provide 70 mg of compound **3.93** ina 70% yield.

Data for **3.93:** (JMO9-200)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.53 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.17-7.14 (m, 2H), 7.11 (d, J = 3.5 Hz, 1H), 7.06 (d, J = 7.7 Hz, 1H), 6.93 (dd, J = 4.2, 4.9 Hz, 1H), 5.17 (d, J = 11.2 Hz, 1H), 5.12 (d, J = 11.2 Hz, 1H), 3.59 (t, J = 7.7 Hz, 2H), 3.15 (s, 1H), 2.44-2.42 (m, 2H), 2.29-2.28 (m, 2H), 1.68-1.66 (m, 4H), 0.91 (t, J = 8.4 Hz, 2H), -0.039 (s, 9H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 174.5, 141.5, 131.1, 130.4, 128.8, 128.7, 126.8, 126.0, 124.6, 124.0, 110.4, 93.7, 87.8, 74.1, 69.8, 69.5, 66.2, 27.6, 27.3, 19.2, 18.5, 17.7, -1.45 (3C)

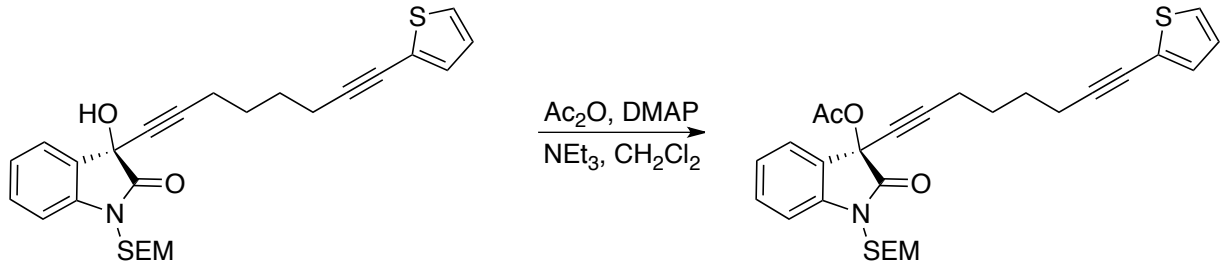
IR (thin film)

3382, 2948, 1753 cm^{-1}

HRMS TOF MS ES+ $C_{26}H_{31}NO_3NaSiS$

Calculated: 488.1692; Found: 488.1664

TLC R_f = 0.31 (20% ethyl acetate/hexanes) [silica gel, UV, p-anisaldehyde]



3.93 **3.94**, 100%

2-oxo-3-(8-(thiophen-2-yl)octa-1,7-diyn-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-3-yl acetate (3.94). A 2-dram vial was charged with alcohol **3.93** (65 mg, 0.139 mmol) and dichloromethane (0.93 mL). To this solution was added 4-dimethylaminopyridine (1.7 mg, 0.0139 mmol), triethylamine (70 μL, 0.502 mmol) and acetic anhydride (32 μL, 0.334 mmol). This solution was left to stir at rt under a nitrogen atmosphere for 1 h at which time all starting material had been consumed based on TLC analysis. The reaction mixture was concentrated and loaded onto a silica gel column. The column was eluted with a gradient of 10-14% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide 70.2 mg of propargyl acetate **3.94** in a quantitative yield.

Data for **3.94:** (JMO9-204)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.41 (dd, *J* = 0.7, 7.7 Hz, 1H), 7.33 (dt, *J* = 0.7, 7.7 Hz, 1H), 7.16 (dd, *J* = 1.4, 5.6 Hz, 1H), 7.11-7.07 (m, 3H), 6.93 (dd, *J* = 3.5, 4.9 Hz, 1H), 5.22 (d, *J* = 11.2 Hz, 1H), 5.16 (d, 11.2 Hz, 1H), 3.73-3.69 (m, 1H), 3.63-3.59 (m, 1H), 2.41 (t, *J* = 6.3 Hz, 2H), 2.30-2.27 (m, 2H), 2.08 (s, 3H), 1.68-1.61 (m, 4H), 0.97-0.92 (m, 2H), -0.035 (s, 9H)

^{13}C NMR δ 171.2, 168.4, 141.9, 131.0, 130.3, 126.8, 126.7, 125.9, 124.0, 123.6, 123.3, 110.3, 93.6, 89.2, 74.02, 73.98, 73.5, 69.9, 66.0, 27.5, 27.1, 20.6, 19.1, 18.5, 17.7, -1.50 (3C)

IR 2949, 2243, 1746, 1613 cm^{-1}

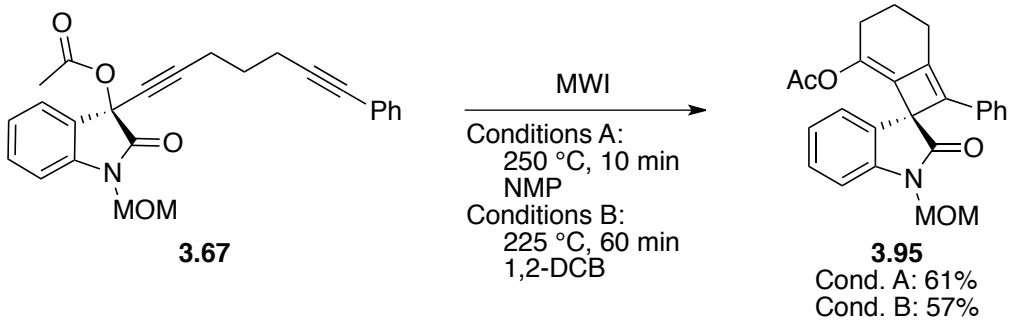
MS *m/z* (%)

530 (20), 487 (10), 486 (10), 330 (100), 302 (10)

HRMS TOF MS ES+ $C_{28}H_{33}NO_4NaSiS$

Calculated: 530.1797; Found: 530.1786

TLC R_f = 0.39 (20% ethyl acetate/hexanes) [silica gel, UV]



3.67 **3.95**
Cond. A: 61%
Cond. B: 57%

General Procedure 5

1'-(methoxymethyl)-2'-oxo-8-phenylspiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl acetate (3.95). In a 2-5 mL Biotage™ microwave vial, propargyl acetate **3.67** (93 mg, 0.232

mmol) was dissolved in 1,2-dichlorobenzene (4 mL). The vial was capped and the solution was irradiated in the microwave at 225 °C for 60 min (time does not include a *ca.* 4 min ramp time). The reaction mixture was applied to a silica gel column and the column was eluted with hexanes (100 mL), then 40% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide 53 mg of spirooxindole **3.95** in 57% yield as a light brown foamy solid.

General Procedure 6

Alternative reaction conditions for the transformation of propargyl acetate 3.67 to spirooxindole 3.95:

In a 0.5 – 2 mL Biotage™ microwave vial, propargyl acetate **3.67** (28 mg, 0.0698 mmol) was dissolved in *N*-methylpyrrolidinone (1.4 mL). The vial was capped and the solution was irradiated in the microwave at 250 °C for 10 min (time does not include a *ca.* 1 min ramp time). The reaction mixture was partitioned between ether (5 mL) and water (5 mL). The ether layer was washed with water (4 x 3 mL). The combined aqueous portions were then extracted with ether (5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate and concentrated. The crude material was purified by silica gel flash chromatography eluting with 40% ethyl acetate/hexanes to afford 17 mg of the title compound **3.95** in 61% yield as a light brown foamy solid.

Data for **3.95**: (JMO5-24)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.29 (td, *J* = 7.7, 1.3 Hz, 1H), 7.20 (ddd, *J* = 7.4, 1.3, 0.6 Hz, 1H), 7.18-7.14 (m, 2H), 7.12-7.08 (m, 2H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.91-6.90 (m, 2H), 5.27 (d, *J* = 11.0 Hz, 1H), 5.25 (d, *J* = 11.0 Hz, 1H), 3.40 (s, 3H), 2.77 (ddd, *J* = 17.1, 7.8,

5.6 Hz, 1H), 2.70 (ddd, *J* = 17.1, 7.1, 5.5 Hz, 1H), 2.43 (ddd, *J* = 16.7, 6.7, 5.2 Hz, 1H), 2.36 (ddd, *J* = 16.7, 7.2, 4.9 Hz, 1H), 2.18-2.03 (m, 2H), 1.78 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 176.2, 167.4, 147.1, 141.9, 137.6, 132.6, 132.2, 128.7, 128.6, 127.2, 127.1, 125.3, 124.4, 123.7, 123.0, 71.7, 62.1, 56.3, 56.3, 27.3, 23.6, 22.2, 20.4

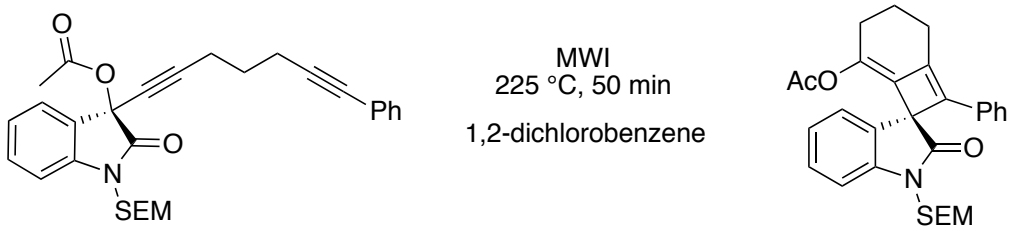
IR (thin film)

2937, 1760, 1728 cm^{-1}

HRMS TOF MS ES+: $C_{25}H_{23}NO_4Na$

Calculated: 424.1525 Found: 424.1509

TLC R_f = 0.28 (40% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.68 **3.96**, 61%

2'-oxo-8-phenyl-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl acetate (3.96). Following General Procedure 5: A 2-5 mL Biotage™ microwave vial was charged with propargyl acetate **3.68** (75 mg, 0.154 mmol) and 1,2-dichlorobenzne (3 mL). The reaction was irradiated at 225 °C for 60 min. The product was isolated by column chromatography eluting with 100 mL of hexanes, followed by a gradient of 5% - 20% ethyl acetate/hexanes. The title compound **3.96** was isolated in 61% yield (45.6 mg) as a light orange foamy solid.

Data for **3.96**: (JMO4-168)

^{1}H NMR (500 MHz, $CDCl_3$)

δ 7.29 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.4 Hz, 1H), 7.16-7.12 (m, 3H), 7.09 (d, *J* = 7.3 Hz, 1H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.90 (d, *J* = 7.5 Hz, 2H), 5.34 (d, *J* = 11.1 Hz, 1H), 5.22 (d, *J* = 11.1 Hz, 1H), 3.71-3.63 (m, 2H), 2.79-2.73 (ddd, *J* = 17.0, 7.0, 7.0 Hz, 1H), 2.69 (ddd, *J* = 17.0, 7.0, 7.0 Hz, 1H), 2.42 (ddd, *J* = 17.0, 5.5, 5.5 Hz, 1H), 2.38-2.32 (ddd, *J* = 17.0, 5.5, 5.5 Hz, 1H), 2.17-2.02 (m, 2H), 1.76 (s, 3H), 0.96 (t, *J* = 8.2 Hz, 2H), -0.04 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$)

δ 176.0, 167.4, 147.1, 142.3, 137.8, 132.7, 132.2, 128.6, 128.6 (2C), 127.2, 127.1, 125.4 (2C), 124.5, 123.7, 122.9, 109.5, 70.0, 66.2, 62.2, 27.3, 23.7, 22.3, 20.5, 17.9, -1.4

IR (thin film)

3056, 2949, 1762, 1730, 1613 cm^{-1}

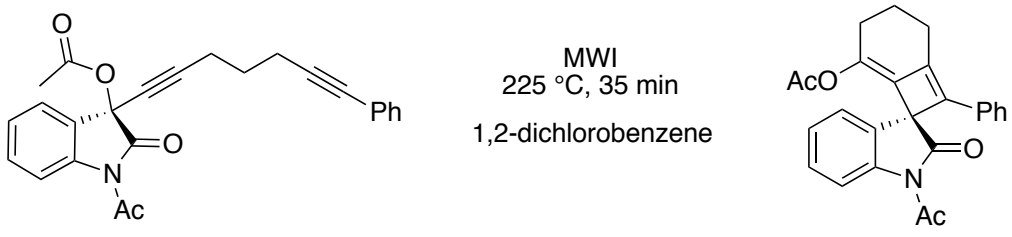
MS TOF MS ES+

m/z (%) 558 (15), 542 (32), 526 (64), 511 (52), 510 (100)

HRMS TOF MS ES+: $C_{29}H_{33}NO_4SiK$

Calculated: 526.1816 Found: 526.1850

TLC R_f = 0.15 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.73 **3.98**, 53%

1'-acetyl-2'-oxo-8-phenylspiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl acetate (3.98). Following General Procedure 5: A 2-5 mL microwave vial was charged with propargyl acetate **3.73** (90 mg, 0.226 mmol) and 1,2-dichlorobenzene (3 mL). The solution was irradiated for 50 min at 225 °C. The reaction mixture was loaded onto a silica gel flash column and eluted with hexanes (100 mL) followed by a gradient of 5-20% ethyl acetate/hexanes to afford 47.4 mg of spirooxindole **3.98** in a 53% yield.

Data for **3.98**: (JMO5-118)

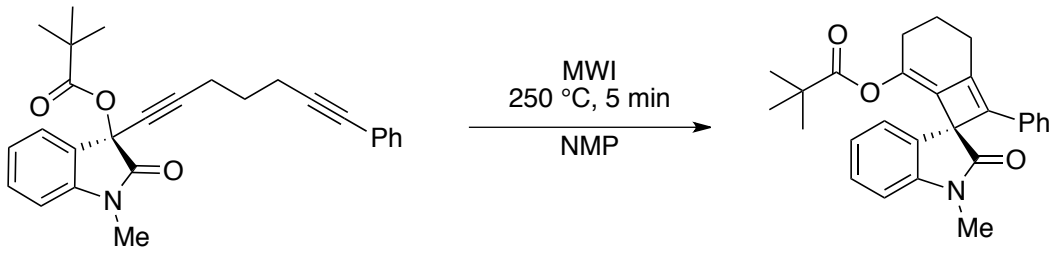
^{1}H NMR (300 MHz, $CDCl_3$)

δ 8.32 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.33 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.21-7.09 (m, 5H), 6.90-6.87 (m, 2H), 2.77-2.71 (m, 2H), 2.75 (s, 3H), 2.37 (t, *J* = 6.0 Hz, 2H), 2.20-2.00 (m, 2H), 1.79 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$)

δ 20.45, 22.19, 23.38, 26.66, 27.24, 77.21, 116.61, 123.12, 124.32, 125.00, 125.24, 126.98, 127.42, 128.74, 128.87, 131.67, 132.18, 138.07, 140.00, 147.61, 167.30, 171.55, 176.54

TLC R_f = 0.17 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.74 **3.99**, 46%

1'-methyl-2'-oxo-8-phenylspiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl pivalate (3.99). Following General Procedure 5: A 0.5-2 mL microwave vial was charged with propargyl

ester **3.74** (17.2 mg, 0.0416 mmol) and 1-methyl-2-pyrrolidinone (0.83 mL). The solution was irradiated for 5 min at 250 °C. After workup, the residue was purified by a silica gel flash column eluting with 22% ethyl acetate/hexanes to provide 7.9 mg of spirooxindole **3.99** in a 46% yield as a lightly colored oil.

Data for **3.99**: (JMO6-12)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.26 (dt, *J* = 0.9, 7.8 Hz, 1H), 7.19-7.08 (m, 4H), 6.96 (dt, *J* = 0.6, 7.5 Hz, 1H), 6.91-6.85 (m, 3H), 2.79 (ddd, *J* = 6.3, 6.9, 17.4 Hz, 1H), 2.68 (ddd, *J* = 6.3, 6.9, 17.4 Hz, 1H), 2.43 (ddd, 16.7, 6.7, 5.0 Hz, 1H), 2.31 (ddd, *J* = 16.7, 6.7, 5.0 Hz, 1H), 2.18-2.04 (m, 2H), 0.831 (s, 9H)

^{13}C NMR (125 MHz, $CDCl_3$)

δ 175.4, 175.2, 147.1, 143.8, 137.1, 132.8, 132.3, 128.54 (2C), 128.53, 127.2, 127.1, 125.5, 125.4 (2C), 123.8, 122.4, 107.8, 61.1, 38.5, 27.2, 27.0, 26.6, 23.9, 22.3

IR (thin film)

2970, 2934, 1747, 1720 cm^{-1}

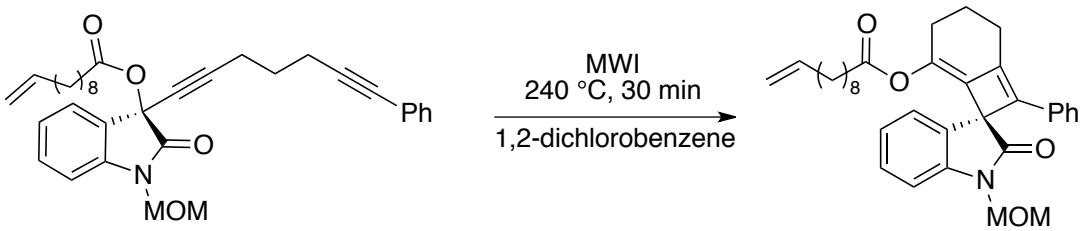
MS *m/z* (%)

436 (10), 351 (10), 350 (100), 112 (20)

HRMS TOF MS ES+ $C_{27}H_{27}NO_3Na$

Calculated: 436.1889; Found: 436.1875

TLC R_f = 0.64 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.75 **3.100**, 56%

1'-(methoxymethyl)-2'-oxo-8-phenylspiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl undec-10-enoate (3.100). Following General Procedure 5: A 0.5-2 mL microwave vial was charged with propargyl ester **3.75** (48 mg, 0.091 mmol) and 1,2-dichlorobenzene (1 mL). The solution was irradiated in an Anton-Paar Monowave microwave synthesizer for 30 min at 240 °C. The crude material was purified by silica gel flash column chromatography eluting with 5-35% ethyl acetate/hexanes to provide 27 mg of **3.100** in a 56% yield.

Data for **3.100**: (JMO9-144)

^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.33-7.28 (m, 1H), 7.24-7.10 (m, 5H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.94 (d, *J* = 7.6 Hz, 2H), 5.92-5.78 (m, 1H), 5.28 (q, *J* = 9.9 Hz, 2H), 5.03 (d, *J* = 18.8 Hz, 1H), 5.00-4.96 (m, 1H), 3.45 (s, 3H), 2.86-2.67 (m, 2H), 2.52-2.32 (m, 2H), 2.19-2.02 (m, 6H), 1.45-1.34 (m, 2H), 1.33-1.11 (m, 8H), 1.07-0.99 (m, 2H)

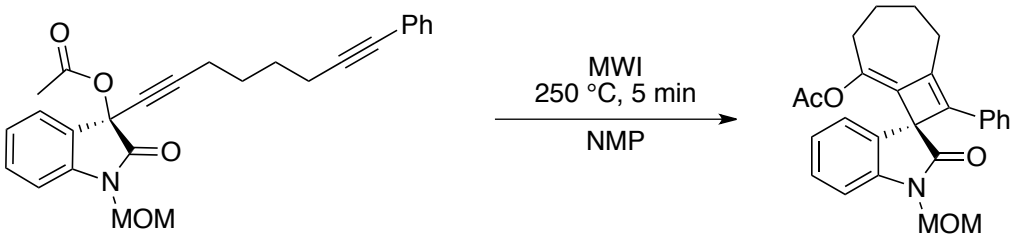
MS *m*/*z* (%)

526 (100), 508 (50), 328 (80), 199 (50), 162 (50)

HRMS TOF MS ES+ $C_{34}H_{40}NO_4$

Calculated: 526.2957; Found: 526.2979

TLC R_f = 0.34 (35% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.81 **3.101**, 48%

1'-(methoxymethyl)-2'-oxo-9-phenylspiro[bicyclo[5.2.0]nona[1(9),6]diene-8,3'-indolin]-6-yl acetate (3.101). A 0.5 – 2 mL microwave vial was charged with propargyl acetate **3.81** (79 mg, 0.190 mmol) and *N*-methylpyrrolidinone (3.8 mL). The vial was capped and the solution was irradiated in the microwave at 250 °C for 5 min (time does not include a *ca.* 1 min ramp time). The reaction mixture was partitioned between ether (10 mL) and water (10 mL). The ether layer was washed with water (4 x 6 mL). The combined aqueous portions were extracted with ether (3 x 5 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The residue was purified by silica gel flash chromatography eluting with a gradient of 21% - 30% ethyl acetate/hexanes to afford 38 mg of spirooxindole **3.101** in 48% yield as a brown oil.

Data for **3.101**: (JMO5-62)

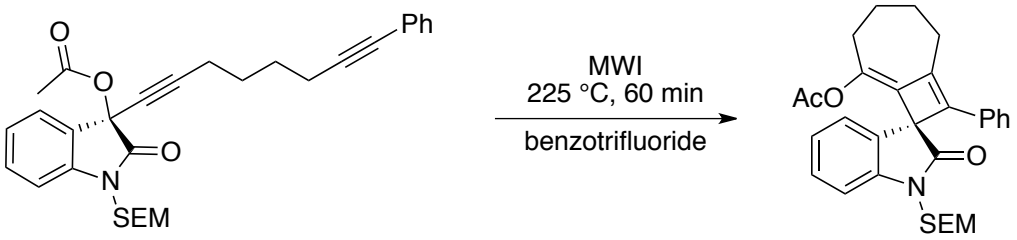
^{1}H NMR (700 MHz, C_6H_6)

δ 7.24 (d, *J* = 7.4 Hz, 1H), 7.10 (d, *J* = 8.0 Hz, 2H), 7.00 (td, *J* = 7.7, 1.2 Hz, 1H), 6.95 (t, *J* = 7.6 Hz, 2H), 6.89-6.87 (m, 2H), 6.83 (td, *J* = 7.5, 0.9 Hz, 1H), 5.16 (d, *J* = 10.9 Hz, 1H), 4.96 (d, *J* = 11.0 Hz, 1H), 3.29 (s, 3H), 2.70 (ddd, *J* = 17.8, 8.0, 3.9 Hz, 1H), 2.47 (ddd, *J* = 18.2, 6.3, 6.3 Hz, 1H), 2.42 (ddd, *J* = 18.2, 6.3, 6.3 Hz, 1H), 2.21 (ddd, *J* = 17.8, 7.8, 3.2 Hz, 1H), 1.62-1.57 (m, 1H), 1.53-1.46 (m, 3H), 1.29 (s, 3H)

^{13}C NMR (75 MHz, $CDCl_3$)

176.3, 168.4, 147.1, 143.0, 140.1, 138.1, 133.8, 130.9, 129.3, 129.0, 128.6, 127.7, 126.8, 125.2, 123.6, 109.6, 71.8, 59.6, 56.7, 34.4, 30.6, 26.3, 26.0, 19.7

TLC R_f = 0.50 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.82 **3.102**, 42%

(*S*)-2'-oxo-9-phenyl-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[bicyclo[5.2.0]nona [1(9),6]diene-8,3'-indolin]-6-yl acetate (3.102). A microwave vial was charged with propargyl acetate **3.82** (60 mg, 0.120 mmol) and benzotrifluoride (2.4 mL). The vial was capped and the solution was irradiated in an Anton-Paar Monowave for 30 min at 225 °C. The reaction mixture was concentrated, applied to a silica gel flash chromatography column, and eluted with 10-20% ethyl acetate/hexanes to provide 25 mg of **3.102** in a 42% yield.

Data for **3.102**: (JMO9-126)

^{1}H NMR (400 MHz, C_6H_6)

δ 7.29 (td, *J* = 7.7, 1.2 Hz, 1H), 7.20-7.10 (m, 5H), 7.03 (td, *J* = 7.5, 0.9 Hz, 1H), 6.97-6.95 (m, 2H), 5.32 (d, *J* = 11.1 Hz, 1H), 5.25 (d, *J* = 11.1 Hz, 1H), 3.75-3.61 (m, 2H), 2.93-2.89 (m, 2H), 2.64-2.59 (m, 1H), 2.31-2.25 (m, 1H), 1.96-1.86 (m, 4H), 1.45 (s, 3H), 1.06-0.89 (m, 2H), -0.02 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 176.2, 168.6, 146.2, 142.0, 138.9, 137.2, 132.5, 129.7, 128.61 (2C), 128.49, 127.7, 126.7, 125.9 (2C), 124.3, 123.1, 109.1, 69.4, 66.1, 58.7, 33.5, 30.1, 25.8, 25.4, 19.6, 17.8, -1.5 (3C)

IR (thin film)

2950, 1745, 1613 cm^{-1}

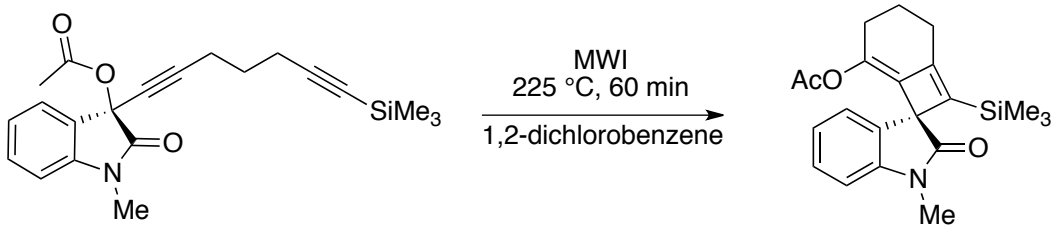
MS *m/z* (%)

524 (100), 464 (40), 324 (50)

HRMS TOF MS ES+ $C_{30}H_{35}NO_4NaSi$

Calculated: 524.2233; Found: 524.2281

TLC R_f = 0.34 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.85 **3.103**, 50%

1'-methyl-2'-oxo-8-(trimethylsilyl)spiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl acetate (3.103). Following General Procedure 5: A 0.5 – 2 mL microwave vial was charged with propargyl acetate **3.85** (29 mg, 0.079 mmol) and 1,2-dichlorobenzene (1.6 mL). The solution was irradiated in the microwave for 50 min at 225 °C. After cooling to room temperature, the reaction mixture was diluted with hexanes (3 mL) and applied to a silica gel column. The column was eluted with hexanes (100 mL), then with a gradient of 10% - 25% ethyl acetate/hexanes. The fractions containing the desired product were concentrated under reduced pressure to furnish 14.5 mg of spirooxindole **3.103** in a 50% yield as a brown oil.

Data for **3.103**: (JMO4-70)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.22 (t, *J* = 7.7 Hz, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 6.96 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 3.24 (s, 3H), 2.50 – 2.45 (m, 1H), 2.41 – 2.37 (m, 1H), 2.28 (t, *J* = 5.6 Hz, 2H), 2.07 – 2.02 (m, 1H), 1.98 – 1.94 (m, 1H), 1.77 (s, 3H), -0.15 (s, 9H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 176.6, 167.2, 163.7, 145.8, 143.4, 131.3, 129.4, 128.0, 124.6, 123.3, 122.0, 107.5, 63.3, 27.1, 26.4, 23.8, 22.9, 20.6, -1.38 (3C)

IR (thin film)

2927, 2854, 1765, 1717, 1612, 1587 cm^{-1}

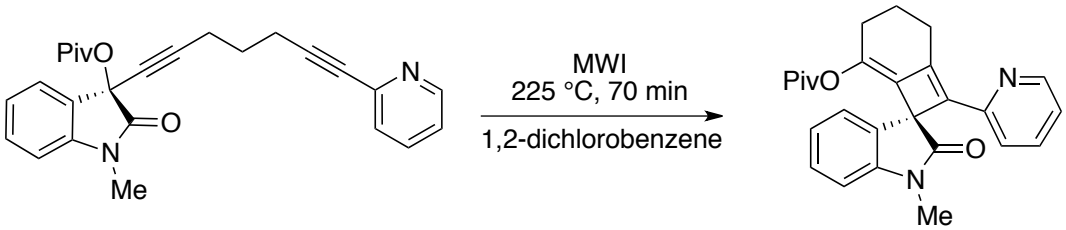
MS TOF MS ES+

m/z (%) 392 (10), 391 (35), 390 (100), 387 (30), 365 (10), 227 (8), 217 (5)

HRMS TOF MS ES+: $C_{21}H_{25}NO_3SiNa$

Calculated: 390.1501 Found: 390.1492

TLC R_f = 0.30 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.92 **3.105**, 40%

1'-methyl-2'-oxo-8-(pyridin-2-yl)spiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl pivalate (3.105). Following General Procedure 5: A 0.5-2 mL microwave vial was charged with

propargyl acetate **3.92** (25 mg, 0.0603 mmol) and 1,2-dichlorobenzene (1.2 mL). The solution was irradiated for 70 min at 225 °C. The solution was loaded onto a silica gel flash chromatography column and eluted with hexanes followed by a gradient of 5-65% ethyl acetate/hexanes to provide 10 mg of spirooxindole **3.105** in a 40% yield.

Data for **3.105**: (JMO9-138)

^{1}H NMR (400 MHz, $CDCl_3$)

δ 8.43 (d, *J* = 3.3 Hz, 1H), 7.42 (t, *J* = 5.7 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.14 (d, *J* = 7.2 Hz, 1H), 6.97-6.92 (m, 2H), 6.85 (d, *J* = 8.0 Hz, 1H), 6.68 (d, *J* =8.0 Hz, 1H), 3.33 (s, 3H), 2.86-2.81 (m, 2H), 2.46-2.41 (m, 1H), 2.36-2.29 (m, 1H), 2.16-2.06 (m, 2H), 0.834 (s, 9H)

IR (thin film)

2928, 1715, 1612 cm^{-1}

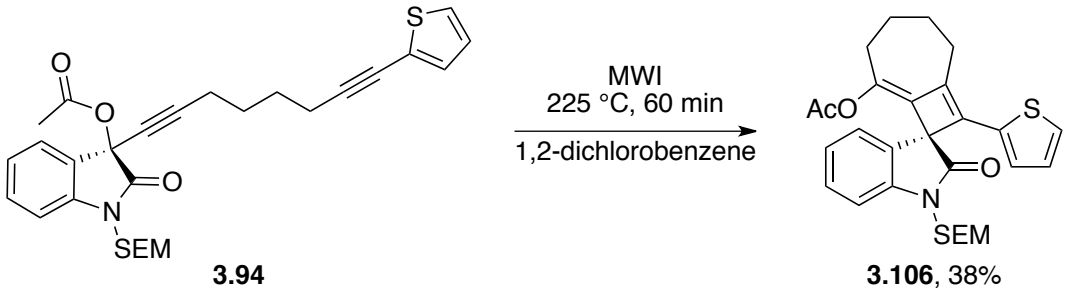
MS *m/z* (%)

415 (10), 331 (20), 313 (100)

HRMS TOF MS ES+ $C_{26}H_{27}N_2O_3$

Calculated: 415.2022; Found: 415.2015

TLC R_f = 0.16 (50% ethyl acetate/hexanes) [Silica gel, UV]



3.94 **3.106**, 38%

2'-oxo-9-(thiophen-2-yl)-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[bicyclo[5.2.0]nona [1(9),6]diene-8,3'-indolin]-6-yl acetate (3.106). Following General Procedure 5: A 0.5-2 mL microwave vial was charged with propargyl acetate **3.94** (35 mg, 0.0689 mmol) and 1,2-dichlorobenzene (1.38 mL). The solution was irradiated for 60 min at 225 °C. The solution was loaded on to a silica gel flash chromatography column and eluted with hexanes followed by 15% ethyl acetate/hexanes to provide 13.4 mg of spirooxindole **3.106** in 38% yield.

Data for **3.106**: (JMO9-208)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.33 (t, *J* = 7.6 Hz, 1H), 7.24 (d, *J* = 4.5 Hz, 1H), 7.20 (d, *J* = 7.3 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.86 (s, 1H), 6.47 (s, 1H), 5.31 (d, *J* = 10.5 Hz, 1H), 5.28 (d, *J* = 10.5 Hz, 1H), 3.73-3.65 (m, 2H), 2.82-2.79 (m, 2H), 2.66-2.62 (m, 1H), 2.34-2.31 (m, 1H), 1.98-1.97 (m, 2H), 1.91-1.89 (m, 2H), 1.48 (s, 3H), 1.05-0.94 (m, 2H), 0.01 (s, 9H)

^{13}C NMR (175 MHz, $CDCl_3$)

δ 175.7, 168.7, 143.6, 142.3, 137.3, 135.1, 133.6, 129.7, 128.8, 127.5, 126.5, 126.0, 124.54, 124.36, 123.1, 109.2, 76.9, 69.5, 66.1, 33.7, 29.5, 25.68, 25.57, 19.7, 17.9, -1.4

IR (thin film)

2920, 1758, 1726, 1612 cm^{-1}

MS *m/z* (%)

530 (100), 487 (35), 486 (60), 330 (60)

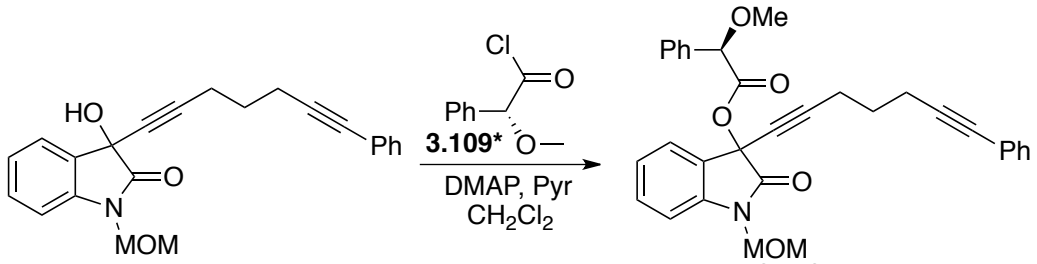
HRMS TOF MS ES+ $C_{28}H_{33}NO_4NaSiS$

Calculated: 530.1797; Found: 530.1744

TLC R_f = 0.31 (20% ethyl acetate/hexanes) [Silica gel, UV, Vanillin Stain]

General Method for the Chiral Shift Analysis

A known amount of racemic substrate was dissolved in 0.5 mL $CDCl_3$ + 0.05% TMS. To this solution was added the chiral lanthanide shift reagent (+)-Eu(hfc)$_3$ (0.05 equiv.) in 0.05 mL $CDCl_3$. A ^{1}H NMR spectrum was then obtained. The shift reagent was continually added in 0.05 equiv. portions until complete resolution of the two diastereomeric complexes was observed in the ^{1}H NMR spectrum. Once appropriate conditions were determined on the racemic substrate, the chiral shift analysis was performed on the enantioenriched substrate using exactly the same quantity of substrate, shift reagent, and solvent.



(2*R*)-1-(methoxymethyl)-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-3-yl 2-methoxy-2-phenylacetate (3.110). A flame-dried single necked 25 mL round bottomed flask was charged with the acid chloride **3.109*** (421 mg, 2.28 mmol) and dichloromethane (7.3 mL). Propargyl alcohol **3.64** (654 mg, 1.82 mmol) was added followed by pyridine (0.293 mL, 3.64 mmol), and finally 4-dimethylaminopyridine (22.2 mg, 0.182 mmol). The reaction was maintained at room temperature for 2 h at which time all starting material had been consumed based on TLC. The

reaction was quenched by adding saturated sodium bicarbonate solution (5 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organic layers were washed with brine (5 mL), dried over magnesium sulfate and concentrated. The crude material was purified by silica gel flash chromatography eluting with a gradient of 100% toluene – 5% ethyl acetate/toluene to afford 244 mg of the least polar diastereomer, 95 mg of the more polar diastereomer, and 205 mg of a mixture in a combined 59% yield.

Data for **3.110**: (JMO6-158)

Less Polar Diastereomer:

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.41 – 7.24 (m, 12H), 7.06 – 7.02 (m, 2H), 5.15 (d, J = 11.2 Hz, 1H), 5.11 (d, J = 11.2 Hz, 1H), 4.81 (s, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 2.43 (t, J = 7.2 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 1.77 (quin, J = 6.8 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 170.6, 168.6, 141.6, 135.1, 131.5 (2C), 130.5, 128.9, 128.6 (2C), 128.2 (2C), 127.6, 127.2 (2C), 126.3, 123.7, 123.6, 123.4, 110.2, 89.3, 88.7, 82.3, 81.3, 74.0, 73.9, 72.0, 57.5, 56.5, 27.1, 18.5, 18.2

IR 2937, 2360, 2244, 1746, 1612 cm^{-1}

MS ESI+ *m/z* (%)

1038 ($[2M+Na+H]^+$, 75), 1037 ($[2M+Na]^+$, 100), 530 ($[M+Na]^+$, 75), 380 (55), 298 (55), 280 (60), 267 (95)

HRMS ESI+: $[M+Na]^+$ $C_{32}H_{29}NO_5Na$

Calculated 530.1943; Found 530.1981

TLC R_f = 0.55 (4 elutions of 20% EtOAc/hexanes) [silica gel, UV]

More Polar Diastereomer

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.37 – 7.33 (m, 8H), 7.29 – 7.25 (m, 3H), 7.02 (d, *J* = 8 Hz, 1H), 6.88 (dt, *J* = 0.8, 7.6 Hz, 1H), 6.69 (dd, *J* = 0.8, 7.6 Hz, 1H), 5.18 (d, *J* = 11.2 Hz, 1H), 5.14 (d, *J* = 10.8 Hz, 1H), 4.89 (s, 1H), 3.42 (s, 3H), 3.38 (s, 3H), 2.43 (t, *J* = 7.2 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 1.77 (quin, *J* = 6.8 Hz, 2H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 171.0, 168.2, 141.7, 135.2, 131.5 (2C), 130.5, 128.9, 128.8, 128.6 (2C), 128.2 (2C), 127.7, 127.5 (2C), 125.6, 123.5, 122.9, 110.2, 89.2, 88.6, 81.6, 81.3, 73.9 (2C), 72.1, 57.5, 56.6, 27.1, 18.5, 18.1

IR 2937, 2244, 1746, 1613 cm^{-1}

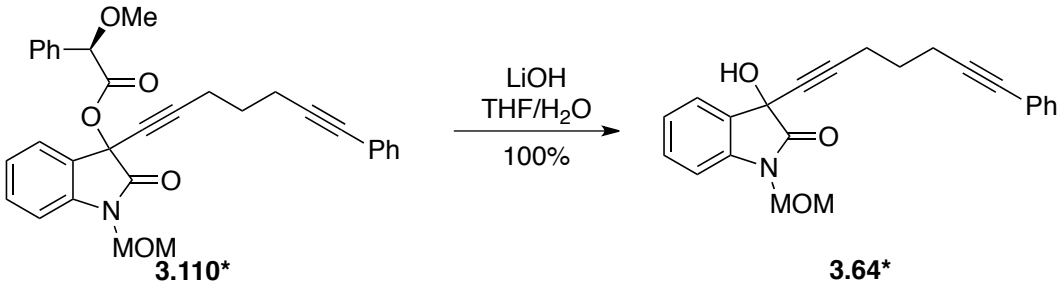
MS ESI+ *m/z* (%)

530 (100), 527 (63), 365 (50), 280 (33), 267 (42)

HRMS ESI+: $[M+Na]^+$ $C_{32}H_{29}NO_5Na$

Calculated 530.1943; Found 530.1896

TLC R_f = 0.50 (4 elutions of 20% EtOAc/hexanes) [silica gel, UV]



3.110* (less polar diastereomer)

3.64*

3-hydroxy-1-(methoxymethyl)-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-2-one (3.64*). A 10 mL round bottomed flask was charged with ester **3.110*** (less polar diastereomer) (140 mg,

0.276 mmol), tetrahydrofuran (1.8 mL), and water (1.8 mL). Lithium hydroxide monohydrate (23.2 mg, 0.552 mmol) was added in one portion and the reaction was left to stir at room temperature for 12 h at which time additional lithium hydroxide monohydrate (23.2 mg, 0.552 mmol) was added and the reaction was maintained at room temperature for 2 h. The reaction mixture was transferred to a separatory funnel and the reaction flask was rinsed with diethyl ether (5 mL) and water (5 mL) and transferred to the separatory funnel. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 3 mL). The combined organic layers were dried over anhydrous magnesium sulfate and concentrated to provide 98.0 mg of propargyl alcohol **3.64*** in 100% yield as a cream colored solid. The product was used without further purification.

Data for **3.64***: (JMO6-160)

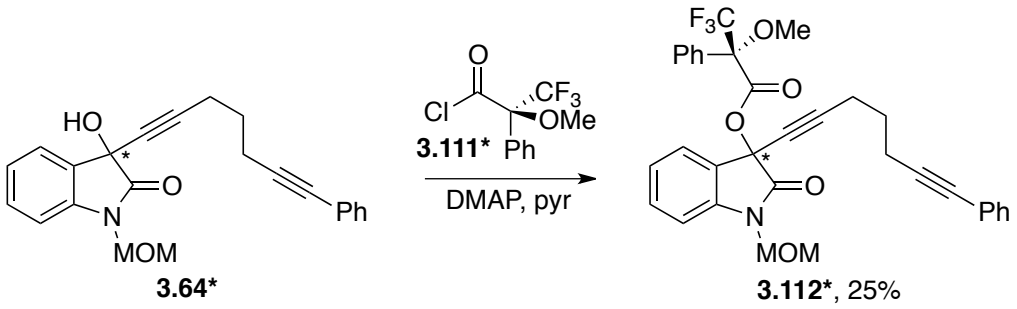
^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.57 (dd, J = 0.9, 7.5 Hz, 1H), 7.40 – 7.35 (m, 3H), 7.31 – 7.27 (m, 3H), 7.19 (dt, J = 0.6, 7.5 Hz, 1H), 7.06 (d, J = 7.5 Hz, 1H), 5.16 (d, J = 11.1 Hz, 1H), 5.12 (d, J = 11.1 Hz, 1H), 3.53 (s, 1H), 3.37 (s, 3H), 2.50 (t, J = 6.9 Hz, 2H), 2.44 (t, J = 6.9 Hz, 2H), 1.82 (quin, J = 7.2 Hz, 2H)

^{13}C NMR (75 MHz, $CDCl_3$)

196.7, 174.7, 141.2, 131.5 (2C), 130.4, 128.7, 128.2 (2C), 127.7, 124.6, 124.1, 123.6, 110.3, 88.7, 87.3, 81.3, 71.7, 69.4, 56.3, 27.3, 18.5, 18.1

TLC R_f = 0.11 (20% EtOAc/hexanes) [silica gel, UV]

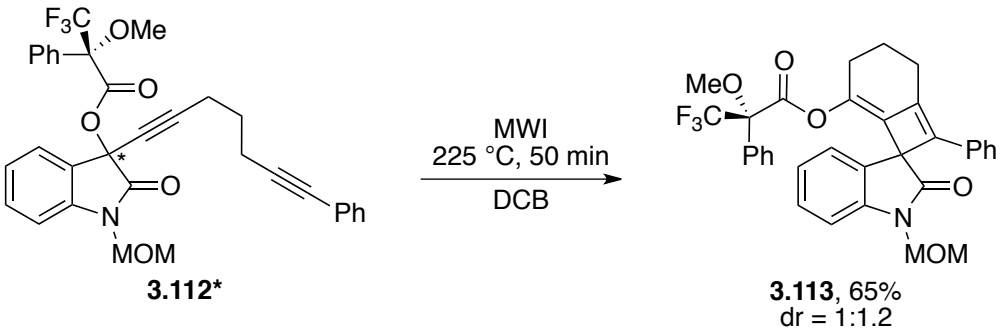


(2*S*)-1-(methoxymethyl)-2-oxo-3-(7-phenylhepta-1,6-diyn-1-yl)indolin-3-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (3.112*). A two-dram vial was charged with propargyl alcohol **3.64*** (30 mg, 0.0836 mmol), acid chloride **3.111*** (25.3 mg, 0.100 mmol), and dichloromethane (0.84 mL). To the stirred solution was added 4-dimethylaminopyridine (1 mg, 0.0084 mmol) and pyridine (13.5 μL, 0.167 mmol). The reaction was left to stir at rt overnight at which time it was diluted with dichloromethane (2 mL) and quenched with saturated aqueous sodium bicarbonate solution (1 mL). The aqueous layer was extracted with dichloromethane (3 x 1 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated. The crude material was loaded onto a silica gel flash chromatography column and eluted with a gradient of 15-25% ethyl acetate/hexanes to provide 12 mg of propargyl ester **3.112*** in a 25% yield.

Data for **3.112*** (JMO6-184)

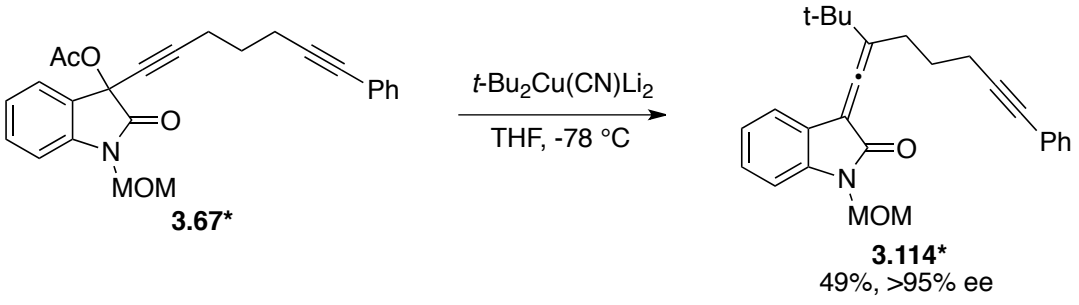
^{1}H NMR (300 MHz, $CDCl_3$)

δ 7.54-7.51 (m, 2H), 7.48-7.46 (m, 1H), 7.40 (td, *J* = 3.5, 2.2 Hz, 3H), 7.37-7.33 (m, 2H), 7.29-7.25 (m, 4H), 7.15 (td, *J* = 7.6, 0.8 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 5.19 (s, 2H), 3.58 (S, 3H), 3.41 (s, 3H), 2.42 (t, *J* = 6.9 Hz, 2H), 2.40 (t, *J* = 6.9 Hz, 2H), 1.77 (quin, *J* = 6.9 Hz, 2H).



3.112* **3.113**, 65% dr = 1:1.2

(2*S*)-1'-(methoxymethyl)-2'-oxo-8-phenylspiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-5-yl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (3.113). A 0.5-2 mL microwave vial was charged with propargyl ester **3.112*** (6.5 mg, 0.113 mmol) and 1,2-dichlorobenzene. The solution was irradiated at 225 °C for 50 min. The reaction mixture was loaded onto a silica gel plug eluting with hexanes followed by a gradient of 5-20% ethyl acetate/hexanes to provide 4.2 mg of spirooxindole **3.113** in a 65% yield. Based on the ^{1}H NMR of the isolated material, a 1:1.2 mixture of diastereomeric products resulted. These products were not separable by flash chromatography. See Appendix A for the ^{1}H NMR spectrum of the diastereomeric mixture.



3.67* **3.114***
49%, >95% ee

3-(2-(*tert*-butyl)-7-phenylhept-1-en-6-yn-1-ylidene)-1-(methoxymethyl)indolin-2-one (3.114*). A 25 mL round bottomed flask was charged with copper(I)cyanide (83.8 mg, 0.935 mmol). The flask was equipped with a magnetic stir bar and a septa and was gently flame dried under vacuum. Upon heating, the copper(I)cyanide changed from a light green color to a light tan color. *Caution: Care must be taken when working with copper(I)cyanide; one must avoid*

any conditions that could generate hydrogen cyanide. The flask was cooled under a positive atmosphere of nitrogen. Tetrahydrofuran (6.7 mL) was then added and the heterogeneous mixture was cooled to -78 °C. *Tert*-butyllithium (1.1 mL of a 1.7 M pentane solution, 1.87 mmol) was then added dropwise over a 20 min period. After 30 min of stirring at -78 °C the solution became paly yellow and homogeneous. To the solution was added propargyl acetate **3.67*** (150 mg, 0.374 mmol) as a solution in tetrahydrofuran (3.7 mL). After 10 min at -78 °C, all starting material had been consumed based on TLC. To quench the reaction, 5 mL of a 9:1 saturated aqueous ammonium chloride: ammonium hydroxide solution was added. The solution was stirred for 1h at which time is became deep blue in color. The aqueous layer was extracted with diethylether (3 x 2 mL). The combined organic layers were dried over magnesium sulfate and concentrated. The crude material was purified by silica gel flash chromatography eluting with a gradient of 10-19% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide allene **3.114*** (72.8 mg, 49%) as a light yellow oil. Also isolated was a small amount of product resulting from a second addition of *tert*-butyl to the central carbon of the allene (R_f = 0.69, 20% ethyl acetate/hexanes). *See text for spectra of the racemic and enantioenriched compounds in the presence of the chiral shift reagent.*

Data for **3.114***: (JMO7-100)

^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.37 – 7.34 (m, 2H), 7.30 – 7.23 (m, 5H), 7.07 (dt, J = 7.6, 0.8 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 5.18 (s, 2H), 3.36 (s, 3H), 2.48 (m, 4H), 1.85 – 1.70 (m, 2H), 1.22 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 203.4, 168.4, 140.0, 131.5 (2C), 128.4, 128.1 (2C), 127.5, 124.5, 123.8, 122.7, 122.3, 121.3, 109.4, 102.2, 89.4, 81.2, 71.4, 56.3, 36.0, 29.4 (3C), 26.8, 26.7, 18.8

IR (thin film)

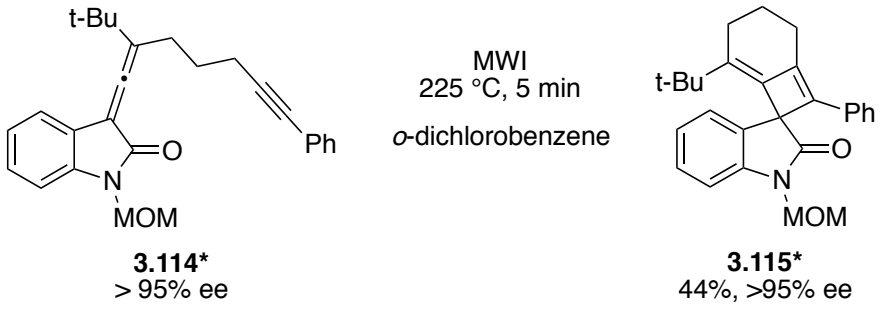
2962, 1945, 1711, 1610 cm^{-1}

HRMS TOF MA ESI+: $C_{27}H_{29}NO_2Na$

Calculated: 422.2096 Found: 422.2122

Rotation $[\alpha]_D^{25} = -3.64$ (*c* 1.1, $CHCl_3$)

TLC $R_f = 0.53$ (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.114*
> 95% ee

3.115*
44%, >95% ee

5-(*tert*-butyl)-1'-(methoxymethyl)-8-phenylspiro[bicyclo[4.2.0]octa[1(8),5]diene-7,3'-indolin]-2'-one (3.115*). A 0.5-2 mL Biotage microwave vial containing a magnetic stir bar was charged with allene **3.114*** (10 mg, 0.025 mmol) and *o*-dichlorobenzene (0.6 mL). The vial was capped and irradiated in the microwave for 5 min at 225 °C. The reaction mixture was loaded onto a silica gel flash column and eluted with hexanes followed by a gradient of 5-17% ethyl acetate/hexanes. The fractions containing the desired product were concentrated to provide 4.4 mg of spirooxindole **3.115*** in 44% yield and >95% ee as a lightly colored oil. *See text for spectra of the racemic and enantioenriched compounds in the presence of the chiral shift reagent.*

Data for **3.115***: (JMO7-124)

^{1}H NMR (400 MHz, $CDCl_3$)

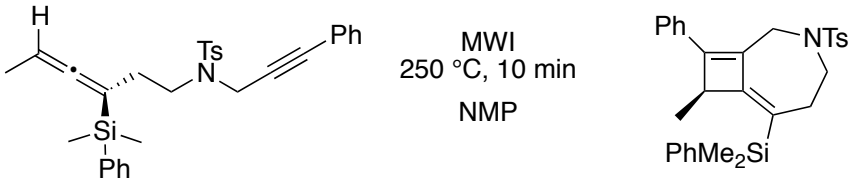
δ 7.31 (dt, *J* = 7.7, 1.2 Hz, 1H), 7.21 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.15-7.11 (m, 3H), 7.07-7.02 (m, 2H), 6.87-6.85 (m, 2H), 5.27 (d, *J* = 10.9 Hz, 1H), 5.18 (d, *J* = 10.9 Hz, 1H), 3.39 (s, 3H), 2.72-2.68 (m, 2H), 2.32-2.19 (m, 2H), 2.12-2.03 (m, 1H), 1.91-1.81 (m, 1H), 0.78 (s, 9H)

^{13}C NMR (100 MHz, $CDCl_3$)

δ 177.3, 149.8, 141.8, 137.6, 133.3, 132.6, 132.0, 129.2, 128.5 (3C), 126.7, 125.2 (2C), 123.6, 123.2, 109.5, 77.2, 71.8, 56.9, 34.8, 28.0 (3C), 25.8, 24.3, 23.1

Rotation $[\alpha]_D^{25} = -3.64$ (*c* 1.1, $CHCl_3$)

TLC $R_f = 0.51$ (2 elutions of 5% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.117*
93% ee

3.118*
93%, 54% ee

6-(dimethyl(phenyl)silyl)-8-methyl-9-phenyl-3-tosyl-3-azabicyclo[5.2.0]nona-1(9),6-diene (3.118*). A 0.5-2 mL microwave vial was charged with allene-yne **3.117*** (4.0 mg, 0.008 mmol) and *N*-methylpyrrolidinone (0.75 mL). The solution was irradiated for 10 min at 250 °C at which time all starting material had been consumed based on TLC analysis. The solution was diluted with water (3 mL) and ether (4 mL). The ether layer was washed with water (5 x 3 mL), dried over magnesium sulfate, and concentrated to provide 3.7 mg of alkylidene cyclobutene **3.118*** in a 93% yield. The enantioselectivity of this transformation was measured by chiral HPLC using a chiral OD column. Based on HPLC analysis the product **3.118*** is formed in 54% ee.

Data for **3.118*** (JMO9-88)

^{1}H NMR (300 MHz, $CDCl_3$)

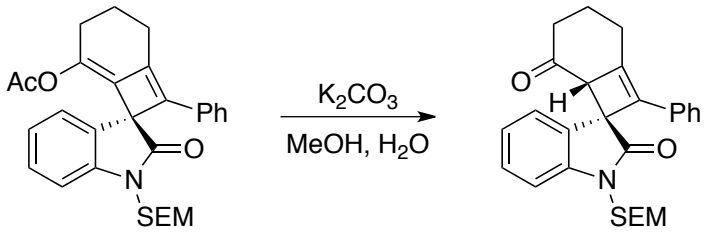
δ 7.70 (d, *J* = 8.2 Hz, 2H), 7.49 (dt, *J* = 4.8, 2.3 Hz, 2H), 7.41-7.28 (m, 8H), 7.20-7.17 (m, 2H), 4.58-4.51 (m, 1H), 4.13-4.07 (m, 1H), 3.74-3.65 (m, 1H), 3.36-3.20 (m, 2H), 2.63-2.52 (m, 1H), 2.47-2.38 (m, 4H), 1.13 (d, *J* = 6.6 Hz, 3H), 0.40 (s, 3H), 0.38 (s, 3H).

MS ESI+ *m/z* (%)

501 (10), 500 (100), 364 (30), 344 (18), 343 (10), 318 (10)

HRMS TOF MA ESI+: $C_{30}H_{34}NO_2SiS$

Calculated: 500.2080 Found: 500.2105



3.96 **3.119**, 100%

8-phenyl-1'-((2-(trimethylsilyl)ethoxy)methyl)spiro[bicyclo[4.2.0]oct[1(8)]ene-7,3'-indoline]-2',5-dione (3.119). A one-dram vial was charged with spirooxindole **3.96** (7 mg, 0.0144 mmol) and methanol (0.5 mL). To this solution was added potassium carbonate (0.17 mL of a 0.1 M solution in water) with stirring. The reaction was left to stir for 10 min at which time water (1 mL) and ether (1 mL) were added. The aqueous layer was extracted with ether (1 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated to provide 6.4 mg of ketone **3.119** in a quantitative yield. The product was pure based on TLC and NMR analysis; therefore further purification was not necessary.

Data for **3.119** (JMO4-182)

^{1}H NMR (300 MHz, $CDCl_3$)

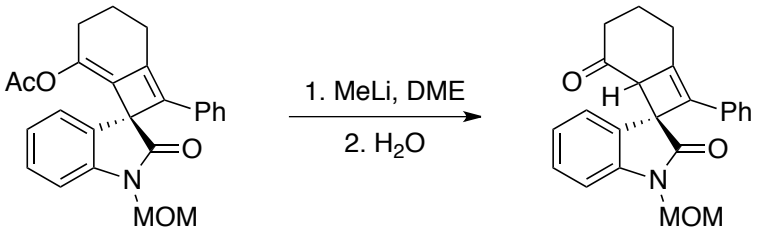
δ 7.51-7.48 (m, 3H), 7.40-7.37 (m, *J* = 1.6 Hz, 2H), 7.22 (td, *J* = 7.7, 1.2 Hz, 1H), 7.02 (dd, *J* = 7.9, 0.5 Hz, 1H), 6.74 (td, *J* = 7.7, 1.0 Hz, 1H), 6.49-6.46 (m, 1H), 6.00 (s, 1H), 5.19 (s, 2H), 3.62 (t, *J* = 8.2 Hz, 2H), 2.59-2.55 (m, 2H), 2.51-2.47 (m, 2H), 2.23-2.15 (m, 2H), 0.95 (t, *J* = 8.2 Hz, 2H), 0.00 (s, 9H)

^{13}C NMR (75 MHz, $CDCl_3$)

δ 199.1, 166.6, 163.5, 151.6, 142.6, 137.6, 129.4 (2C), 127.8 (2C), 126.7, 124.3, 123.3, 122.1, 121.6, 109.6, 77.2, 69.2, 66.1, 51.5, 37.3, 29.1, 23.1, 17.8, -1.4 (3C)

IR 2950, 1711, 1674, 1607 cm^{-1}

TLC R_f = 0.22 (20% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]



3.95 **3.123**, 92%

1'-(methoxymethyl)-8-phenylspiro[bicyclo[4.2.0]oct[1(8)]ene-7,3'-indoline]-2',5-dione (3.123). A 5 mL round bottomed flask under a nitrogen atmosphere was charged with spirooxindole **3.95** (25 mg, 0.077 mmol) and tetrahydrofuran (1.5 mL). This solution was cooled to 0 °C with stirring at which time methyllithium (0.096 mL of a 1.6 M solution in Et_2O, 0.154 mmol) was added via syringe. After 15 min, water (2 mL) was added to quench the reaction. The mixture was diluted with ether (5 mL), the layers were separated and the aqueous layer was extracted with ether (3 x 3 mL). The combined organic layers were washed with brine, dried over

magnesium sulfate, and concentrated. The residue was purified by silica gel flash chromatography eluting with 45% ethyl acetate/hexanes to provide 20 mg of the title compound **3.123** in a 92% yield as a light yellow oil.

Data for **3.123** (JMO6-62)

^{1}H NMR (700 MHz, $CDCl_3$)

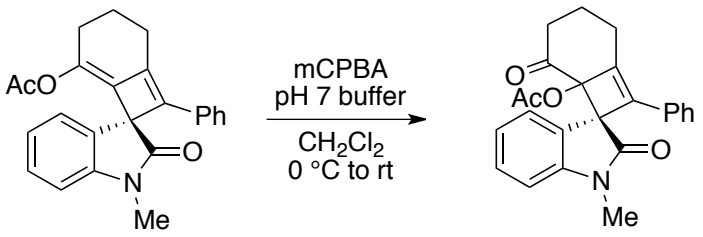
δ 7.49-7.48 (m, 3H), 7.38-7.37 (m, 2H), 7.20 (td, *J* = 7.7, 1.2 Hz, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.73 (td, *J* = 7.7, 1.0 Hz, 1H), 6.48-6.46 (m, 1H), 6.00 (s, 1H), 5.15 (s, 2H), 3.37 (s, 3H), 2.56 (td, *J* = 5.9, 1.4 Hz, 2H), 2.48 (t, *J* = 6.7 Hz, 2H), 2.18 (quin, *J* = 5.6 Hz, 2H).

^{13}C NMR (175 MHz, $CDCl_3$)

δ 199.2, 166.8, 163.4, 142.3, 137.5, 129.81, 129.69, 129.4, 127.8, 126.7, 124.2, 123.4, 122.3, 121.6, 109.5, 71.2, 56.4, 37.3, 29.0, 23.1

TLC R_f = 0.43 (50% EtOAc/hexanes) [silica gel, UV, *p*-anisaldehyde stain]

Other See Appendix A for attached HMBC, HMQC, and COSY spectra



3.58 **3.127**, 48%

1'-methyl-2',5-dioxo-8-phenylspiro[bicyclo[4.2.0]oct[1(8)]ene-7,3'-indolin]-6-yl acetate (3.127). A 10 mL round bottomed flask was charged with the spirooxindole (20 mg, 0.539 mmol), dichloromethane (2.4 mL), and pH 7 phosphate buffer (3 mL). Meta-chloroperoxybenzoic acid (10.3 mg, 0.0594 mmol) was added in one portion. The reaction was

left to stir at rt for 1 h at which time all starting material had been consumed based on TLC. The reaction mixture was then diluted with dichloromethane (5 mL) and quenched by adding saturated sodium sulfite solution (3 mL). The layers were separated and the organic layer was washed with sodium bicarbonate, dried over magnesium sulfate, and concentrated. The crude material was purified by silica gel flash chromatography eluting with a gradient of 10-30% ethyl acetate/hexanes to provide 10 mg of the title compound **3.127** in a 48% yield.

Data for **3.127** (JMO9-108)

^{1}H NMR (700 MHz, $CDCl_3$)

δ 7.46-7.43 (m, 5H), 7.22 (td, J = 7.7, 1.2 Hz, 1H), 6.79 (d, J = 7.7 Hz, 1H), 6.72 (td, J = 7.7, 1.0 Hz, 1H), 6.62-6.61 (m, 1H), 3.25 (s, 3H), 2.88-2.84 (m, 1H), 2.69-2.56 (m, 3H), 2.40-2.35 (m, 1H), 2.14-2.08 (m, 1H), 2.03 (s, 3H).

^{13}C NMR (175 MHz, $CDCl_3$)

δ 191.0, 168.0, 166.2, 146.4, 144.2, 136.7, 129.84, 129.76, 129.2, 128.4, 125.3, 123.4, 121.66, 121.47, 108.1, 57.8, 37.8, 30.3, 29.7, 26.0, 22.9, 20.3

MS ESI+ *m/z* (%)

347 (10), 346 (40), 329 (30), 328 (100), 317 (10), 300 (20)

HRMS TOF MA ES+: $C_{24}H_{22}NO_4$

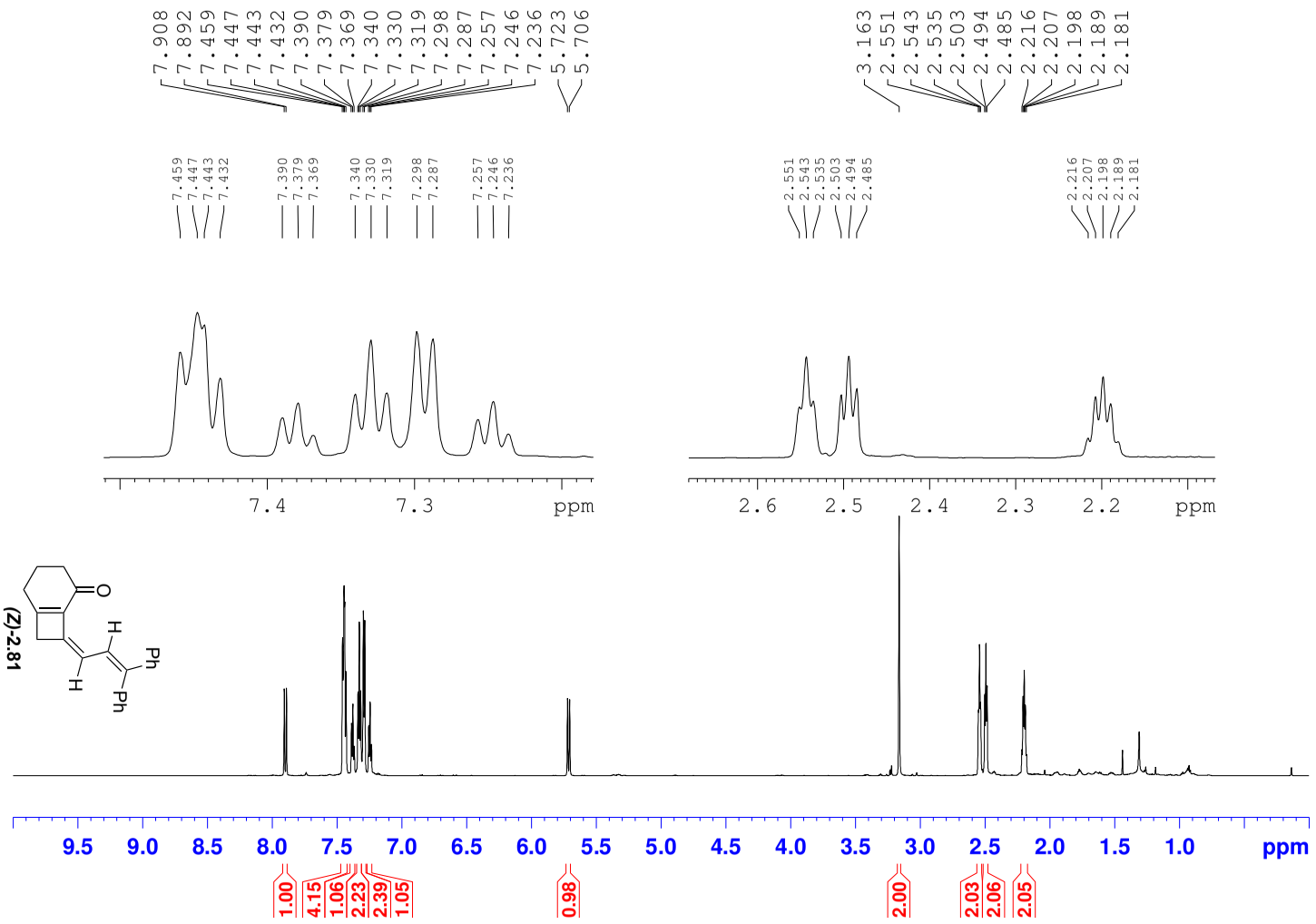
Calculated: 388.1549 Found: 388.1561

TLC R_f = 0.4 (35% EtOAc/hexanes) [silica gel, UV]

APPENDIX

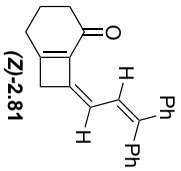
NMR Spectra of Unpublished and Select Compounds

JMO4-72 Col 2 Frn 15-19
NMR 700 - microprobe

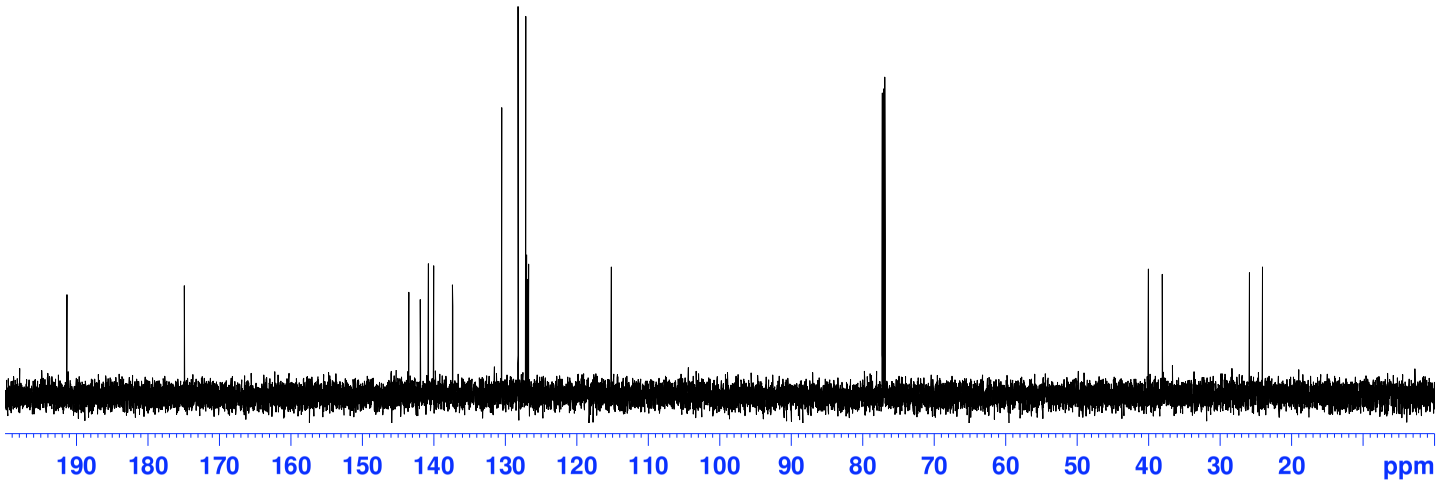


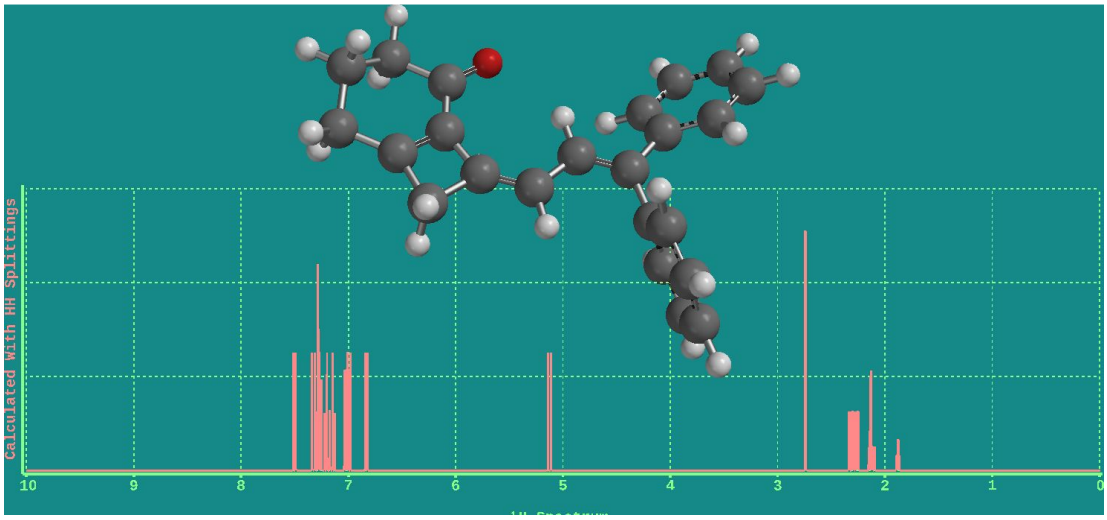
JMO4-72 Col 2 Frn 15-19
NMR 700 - microprobe

191.31
174.94
143.52
141.91
140.80
140.06
137.40
130.55
128.24
128.23
127.16
127.05
127.00
126.78
115.21
77.28
77.10
76.92
40.07
38.11
25.93
24.11

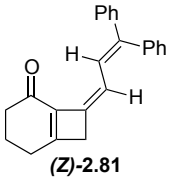


(Z)-2.81





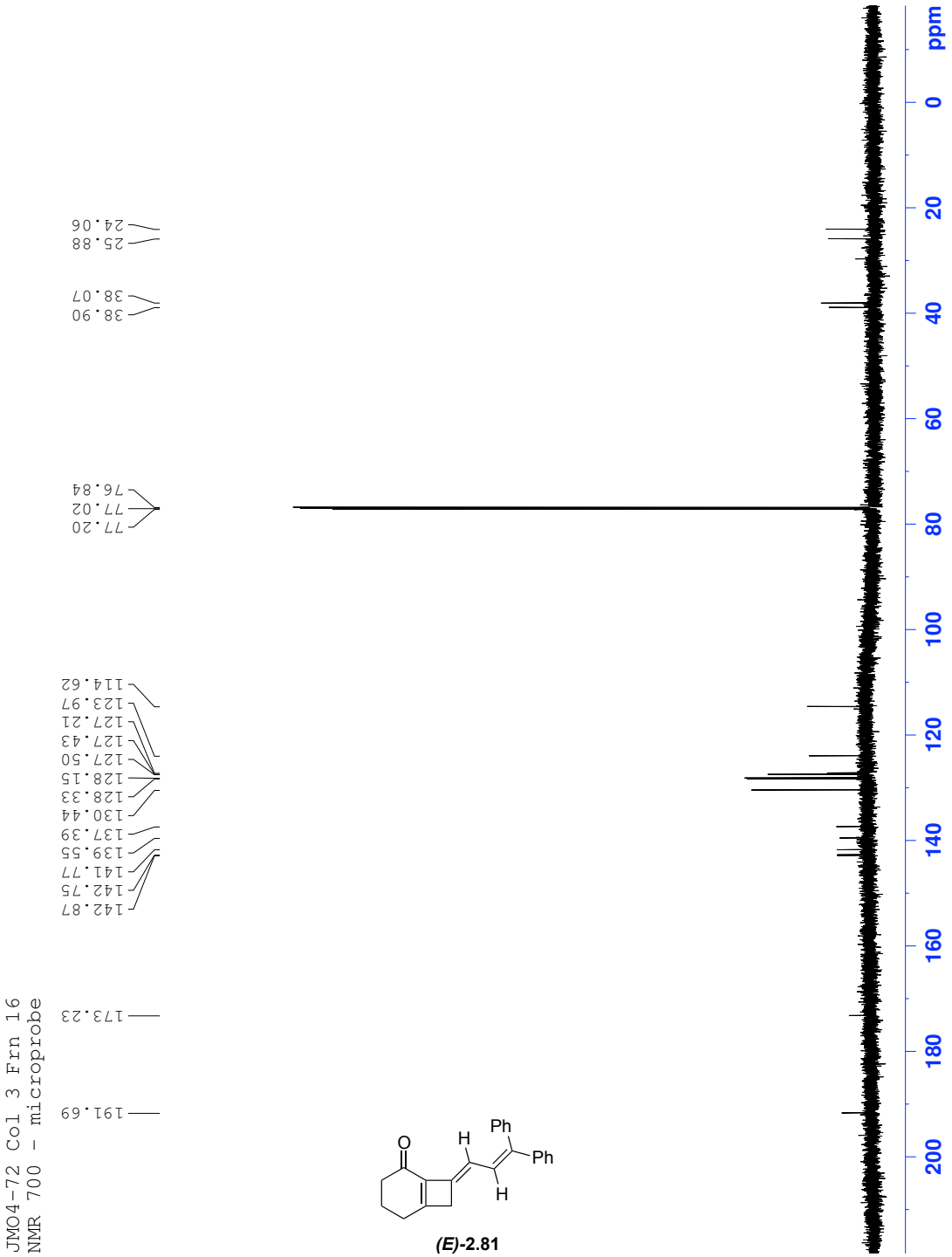
Spartan 2008 1H NMR Prediction



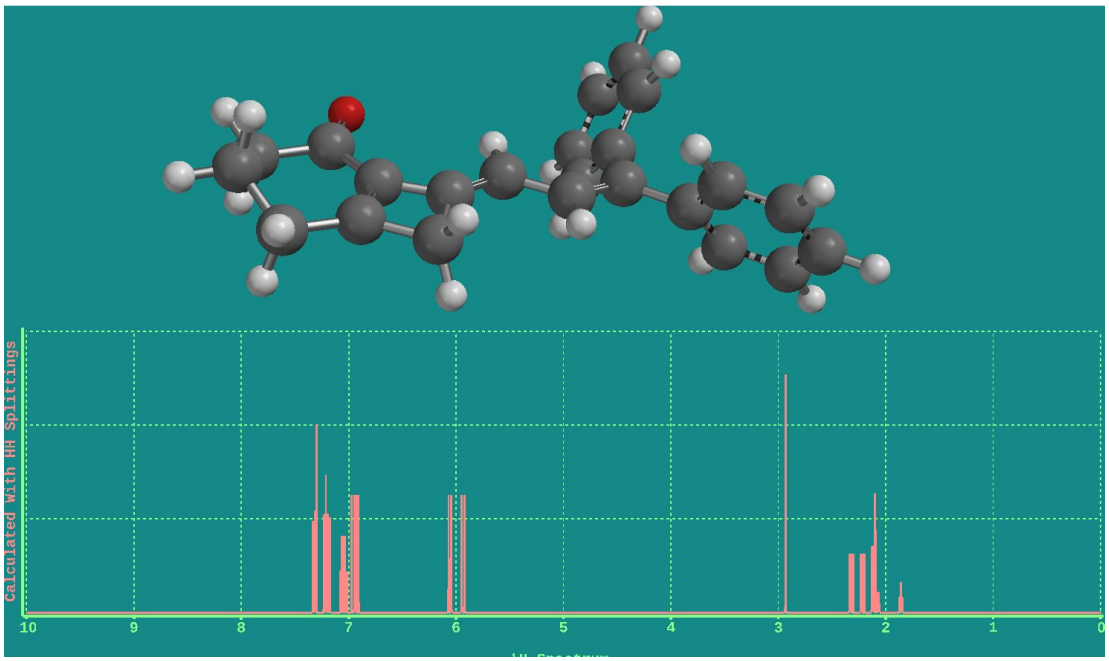
***(Z)*-2.81**

JMO4-72 Col 3 Frn 16
NMR 700 - microprobe
ppm
2.24
2.14
2.07
2.06
2.02
0.97
1.00
3.72
5.86
1.25
2.37
O
H
Ph
Ph
H

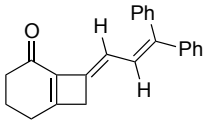
(E)-2.81


JMO4-72 Col 3 Frn 16
NMR 700 - microprobe
191.69
173.23
142.87
142.75
141.77
139.55
137.39
130.44
128.33
128.15
127.50
127.43
127.21
123.97
114.62
77.20
77.02
76.84
38.90
38.07
25.88
24.06
O
H
Ph
Ph
H
ppm
0
20
40
60
80
100
120
140
160
180
200

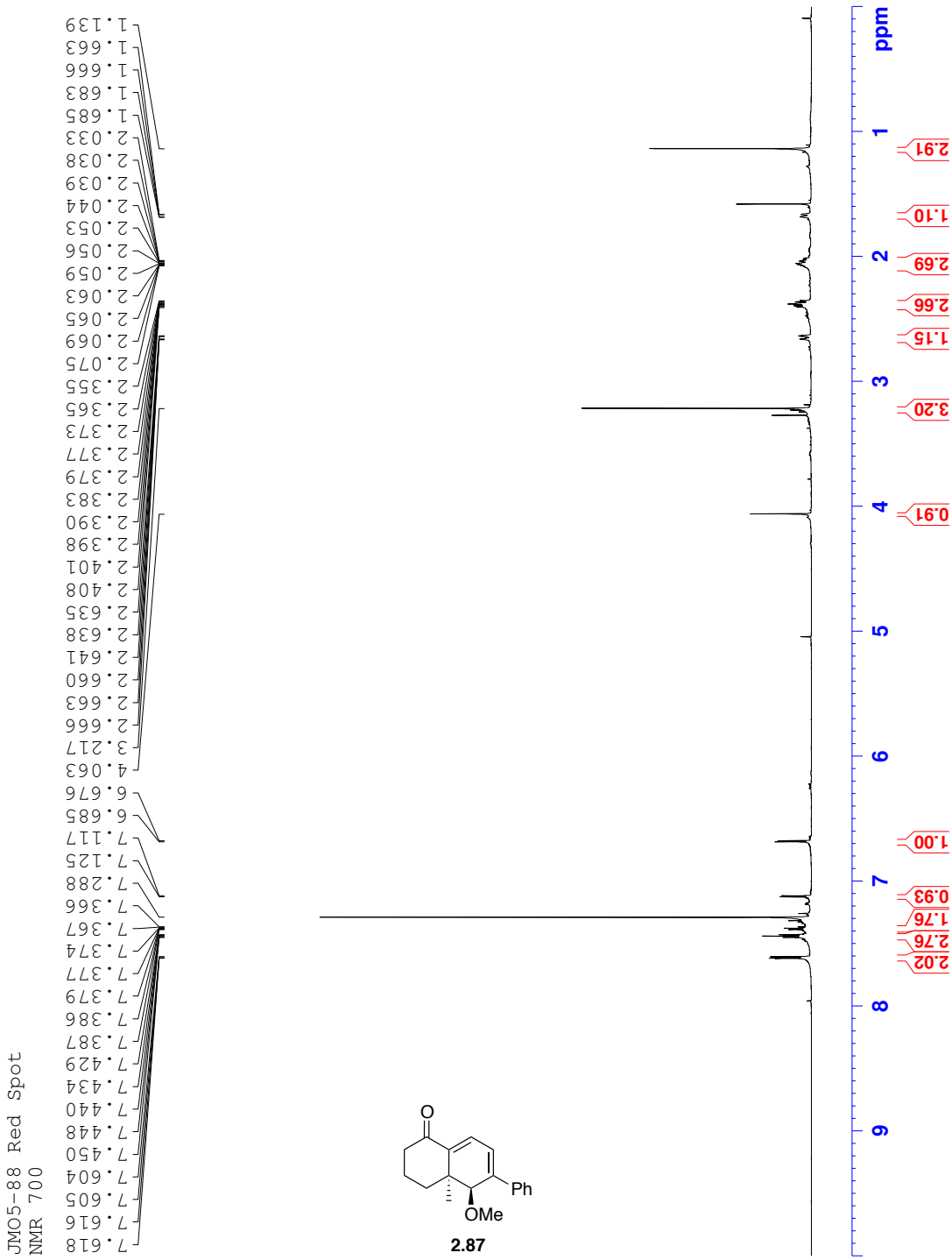
***(E)*-2.81**

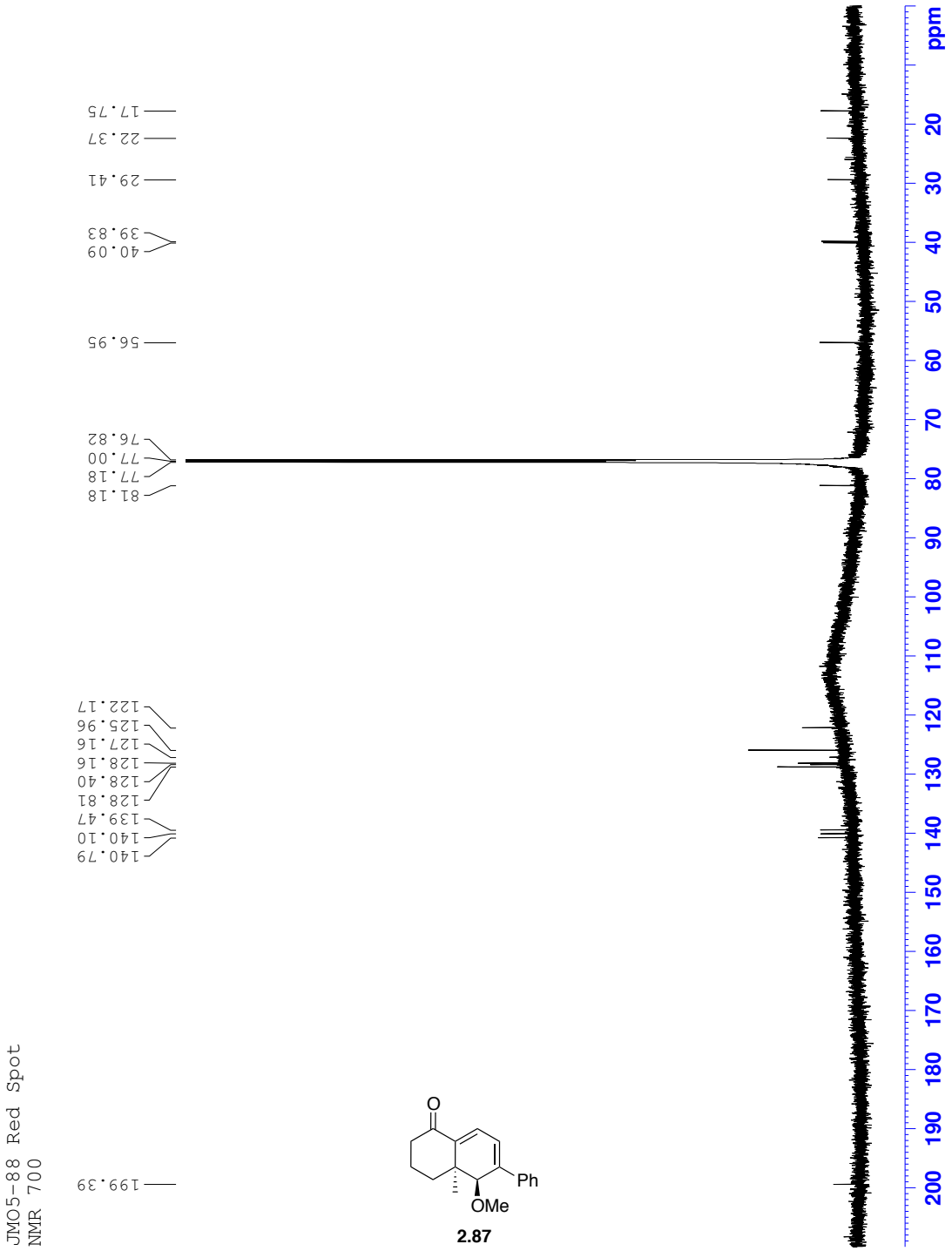


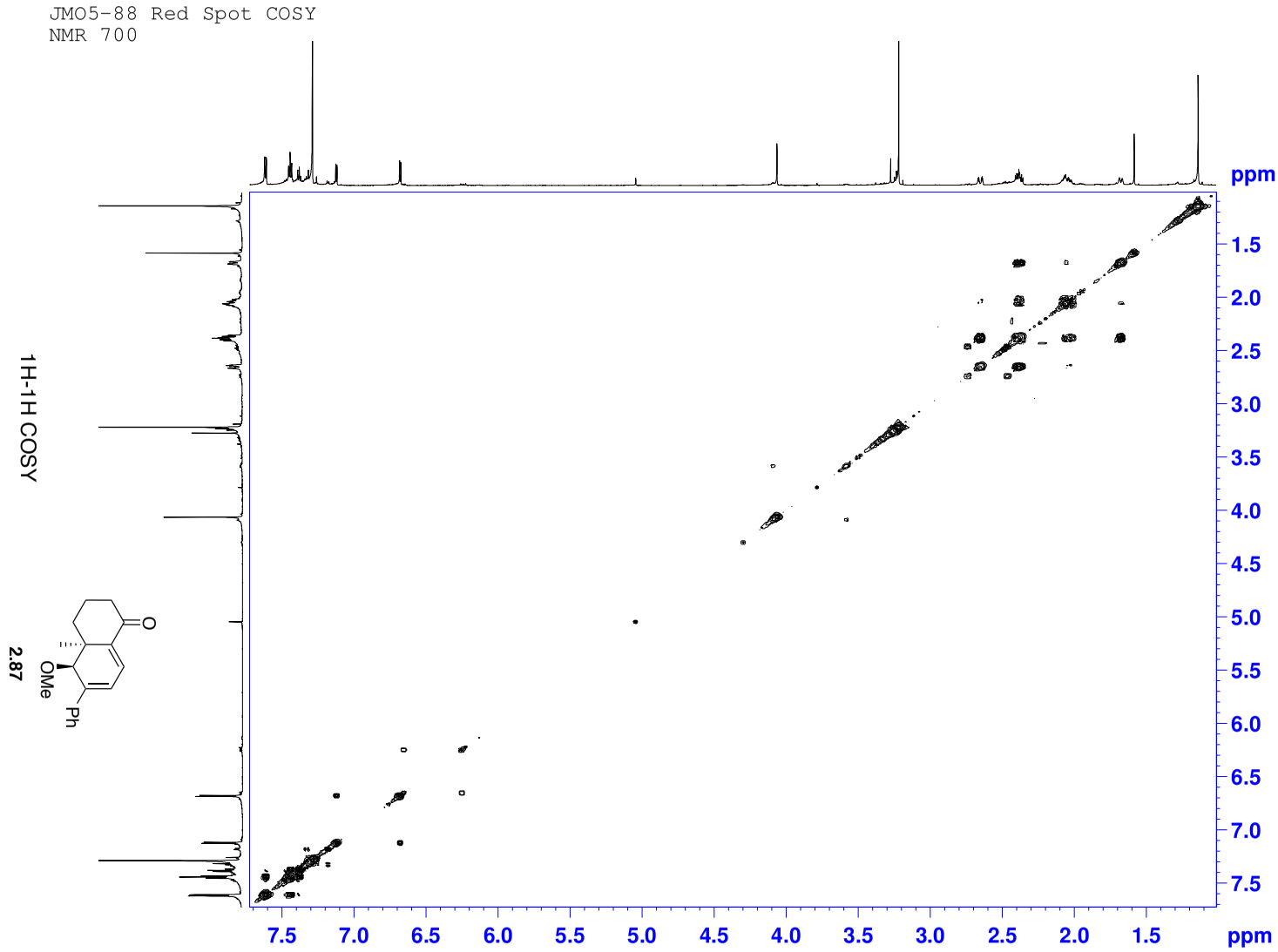
Spartan 2008 1H NMR Prediction

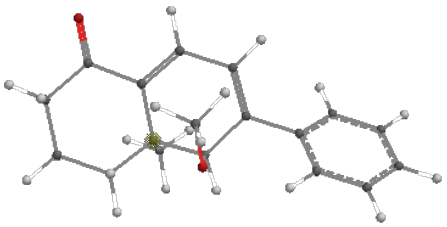


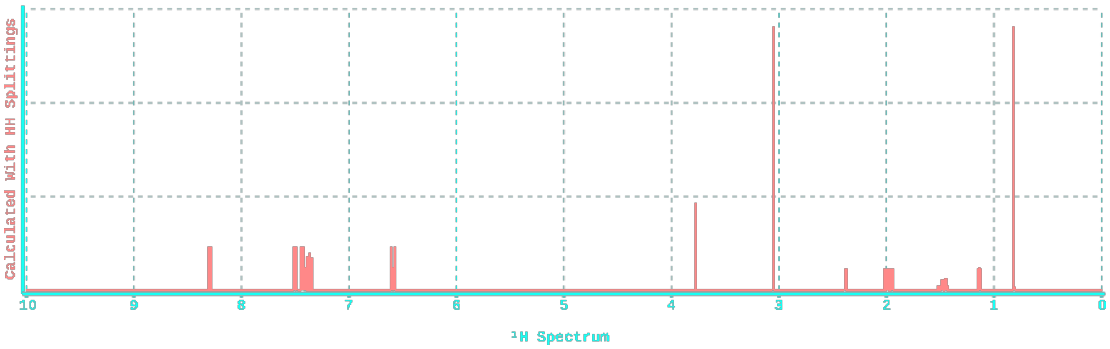
***(E)*-2.81**


JMO5-88 Red Spot
NMR 700
7.618
7.616
7.605
7.604
7.450
7.448
7.440
7.434
7.429
7.387
7.386
7.379
7.377
7.374
7.367
7.366
7.288
7.125
7.117
6.685
6.676
4.063
3.217
2.666
2.663
2.660
2.641
2.638
2.635
2.408
2.401
2.398
2.390
2.383
2.379
2.377
2.373
2.365
2.355
2.075
2.069
2.065
2.063
2.059
2.056
2.053
2.044
2.039
2.038
2.033
1.685
1.683
1.666
1.663
1.139
O
Ph
OMe
2.87
ppm
1
2
3
4
5
6
7
8
9
2.91
1.10
2.69
2.66
1.15
3.20
0.91
1.00
0.93
1.76
2.76
2.02

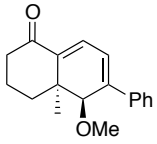

JMO5-88 Red Spot
NMR 700
17.75
22.37
29.41
39.83
40.09
56.95
76.82
77.00
77.18
81.18
122.17
125.96
127.16
128.16
128.40
128.81
139.47
140.10
140.79
199.39
O
Ph
OMe
2.87
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200


JMO5-88 Red Spot COSY
NMR 700
1H-1H COSY
2.87
OMe
Ph
O
ppm
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm

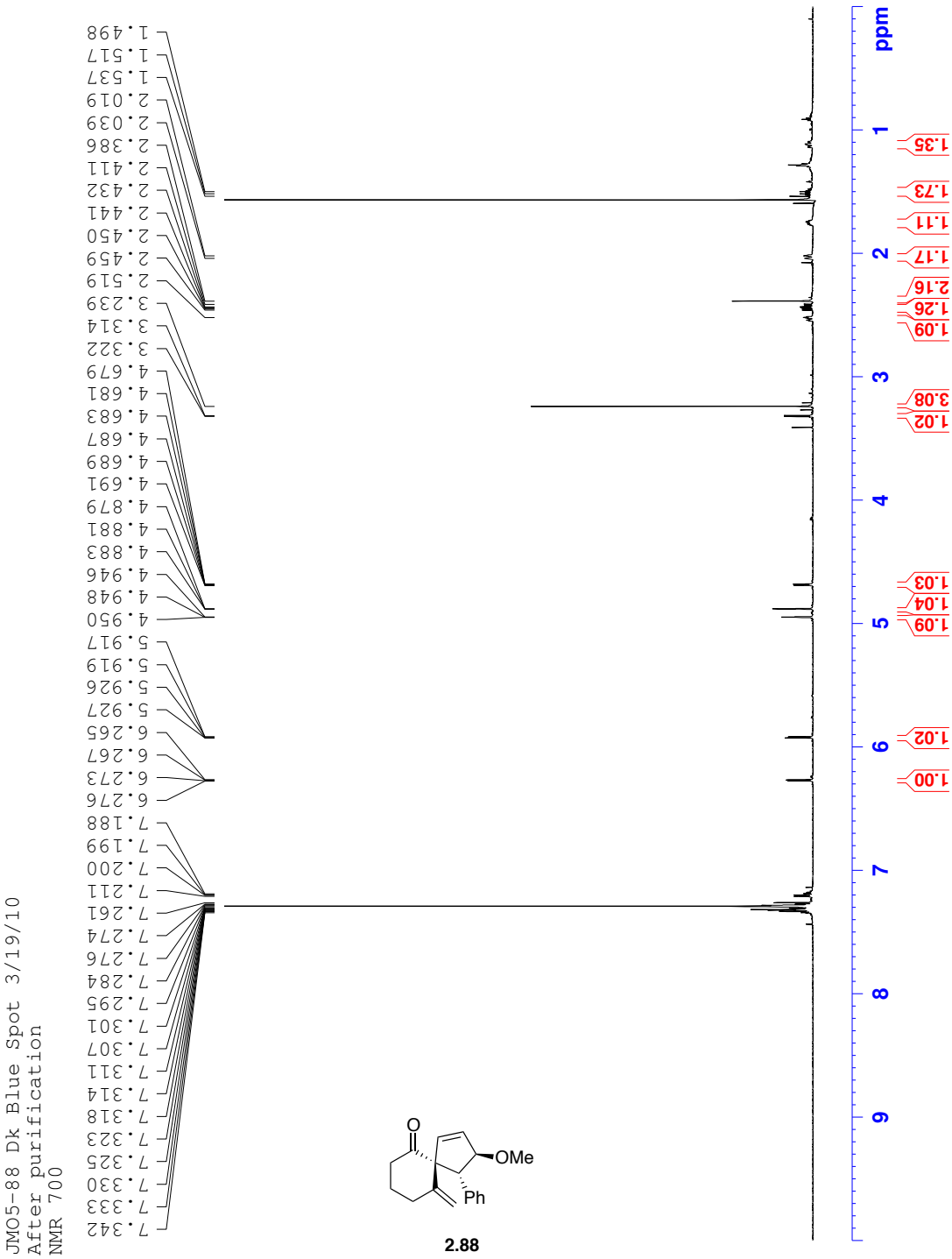


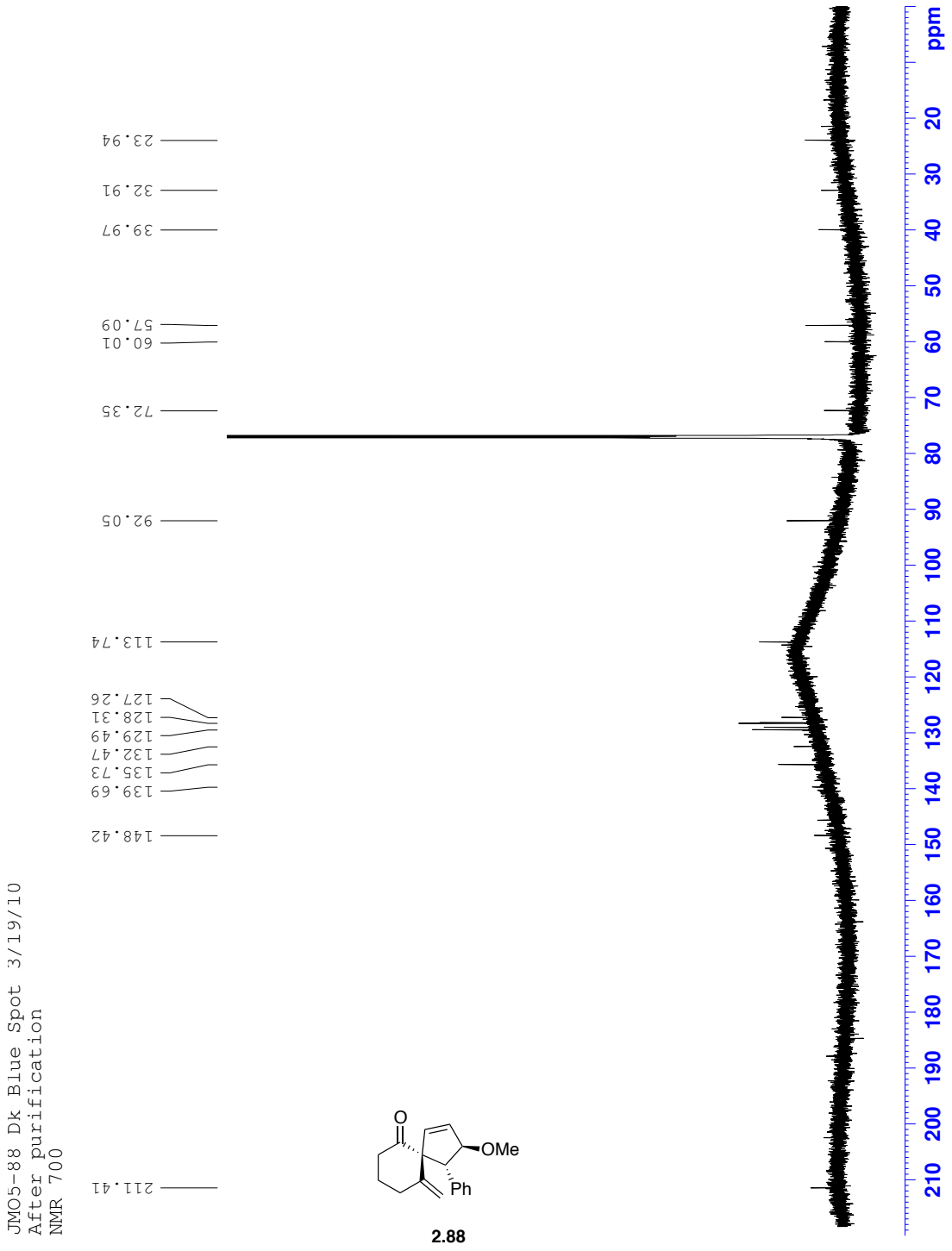


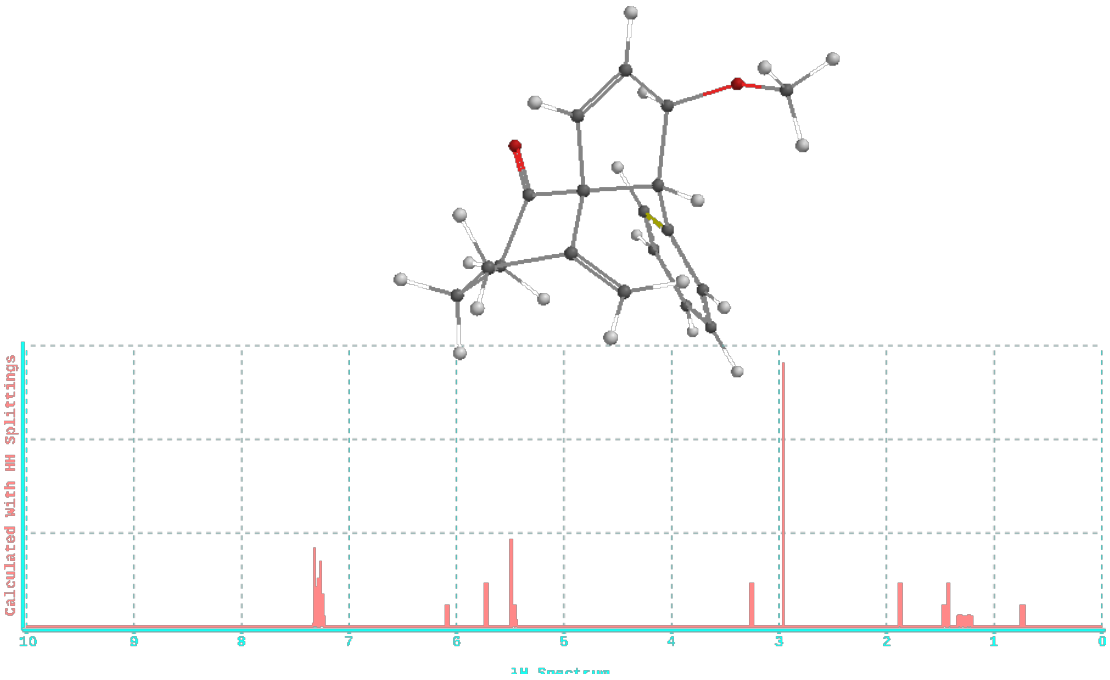
Spartan 2008 1H NMR Prediction



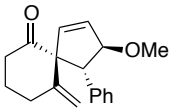
2.87


JMO5-88 Dk Blue Spot 3/19/10
After purification
NMR 700
7.342
7.333
7.330
7.325
7.323
7.318
7.314
7.311
7.307
7.301
7.295
7.284
7.276
7.274
7.261
7.211
7.200
7.199
7.188
6.276
6.273
6.267
6.265
5.927
5.926
5.919
5.917
4.950
4.948
4.946
4.883
4.881
4.879
4.691
4.689
4.687
4.683
4.681
4.679
3.322
3.314
3.239
2.519
2.459
2.450
2.441
2.432
2.411
2.386
2.039
2.019
1.537
1.517
1.498
O
OMe
Ph
2.88
ppm
1
2
3
4
5
6
7
8
9
1.35
1.73
1.11
1.17
2.16
1.26
1.09
3.08
1.02
1.03
1.04
1.09
1.02
1.00

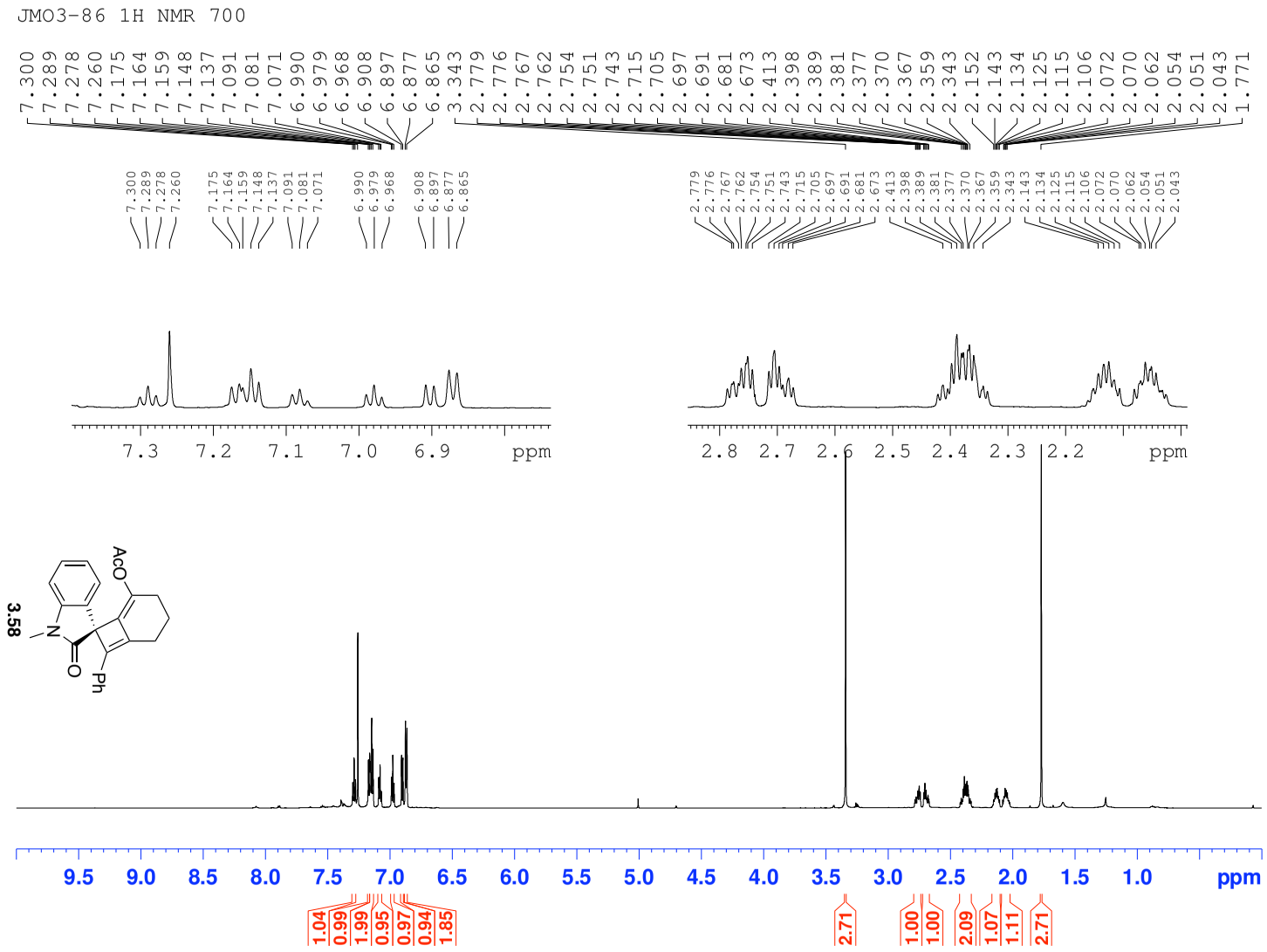

JMO5-88 Dk Blue Spot 3/19/10
After purification
NMR 700
211.41
148.42
139.69
135.73
132.47
129.49
128.31
127.26
113.74
92.05
72.35
60.01
57.09
39.97
32.91
23.94
O
OMe
Ph
2.88
ppm
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

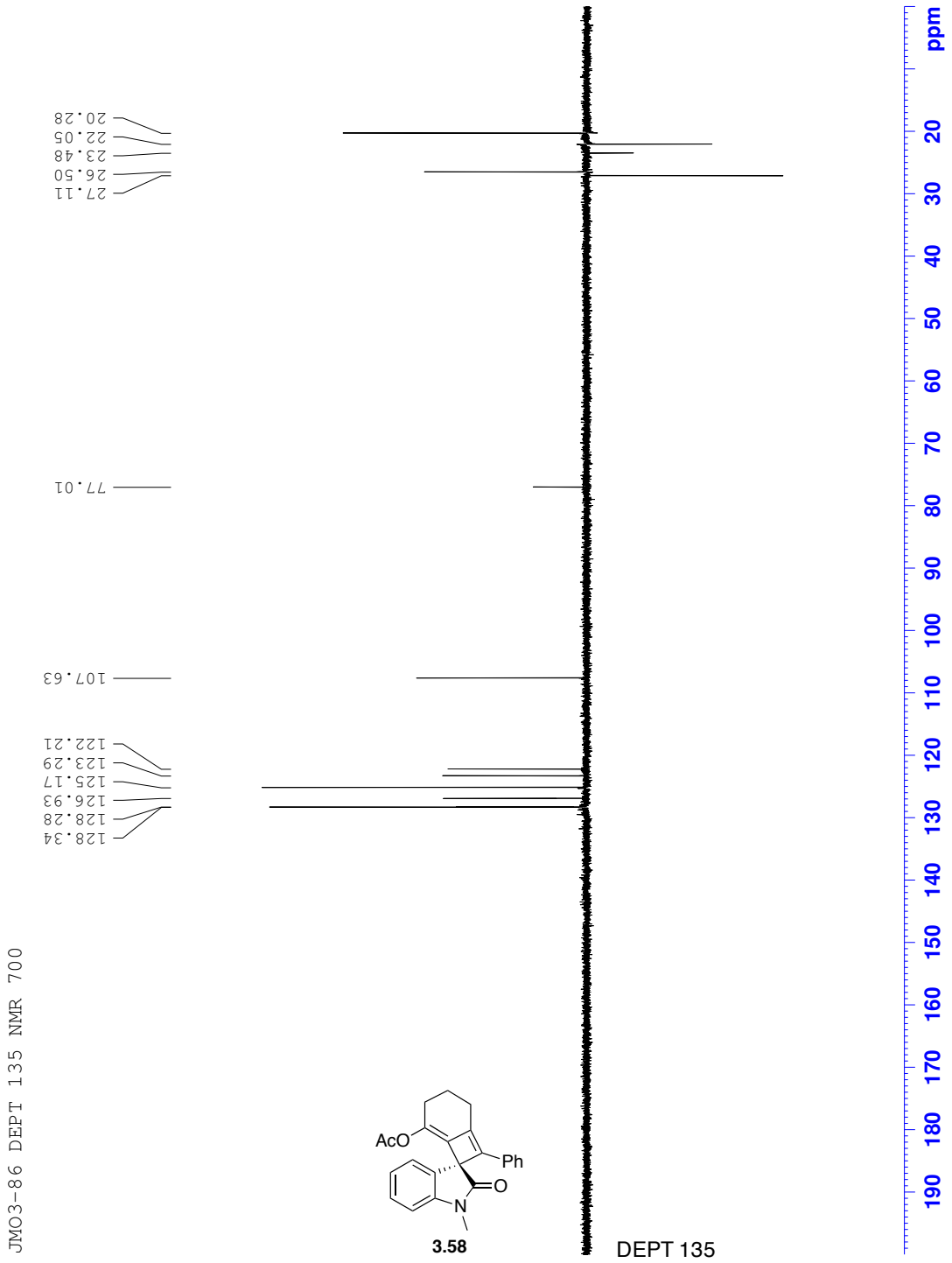


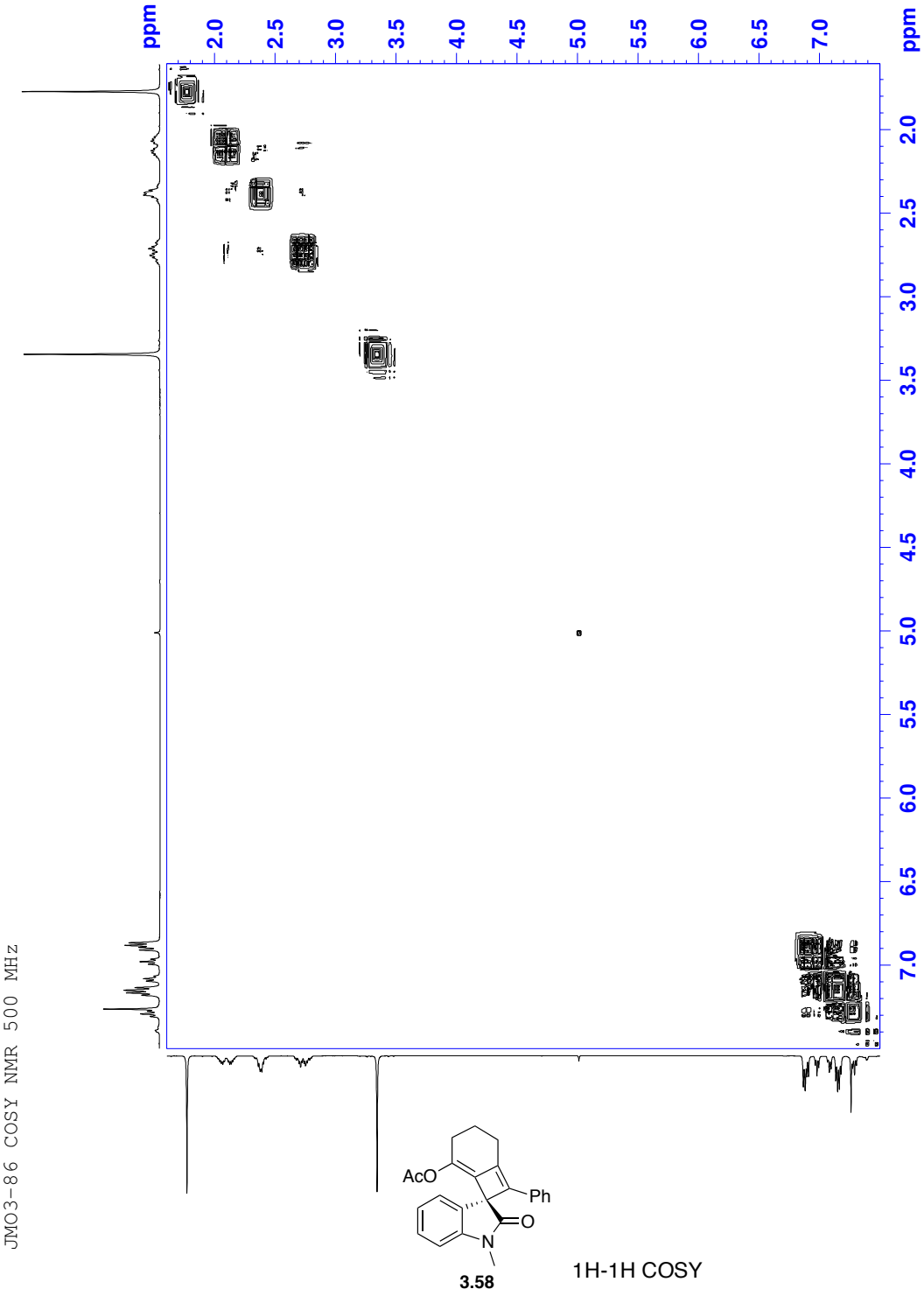
Spartan 2008 1H NMR Prediction

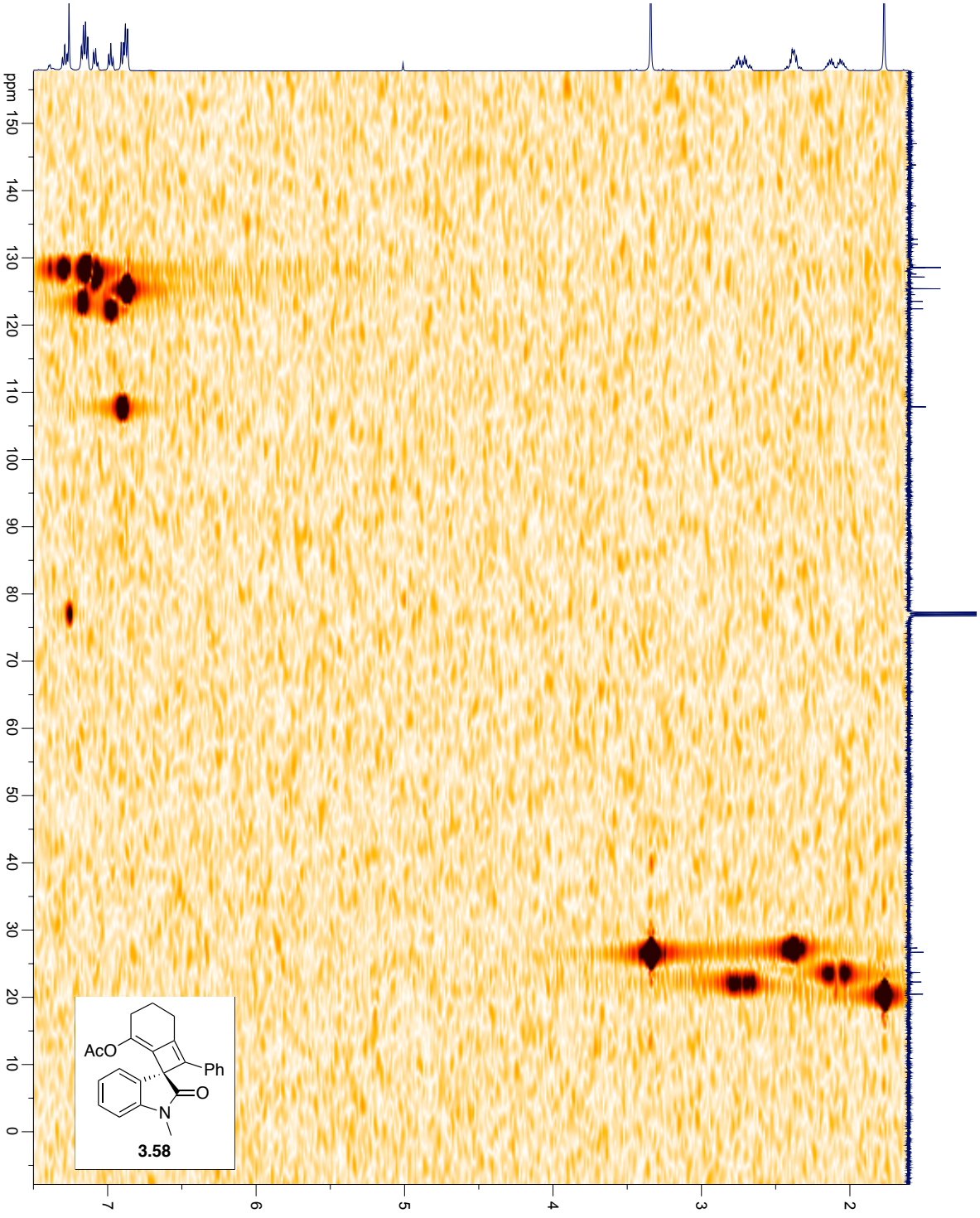


2.88

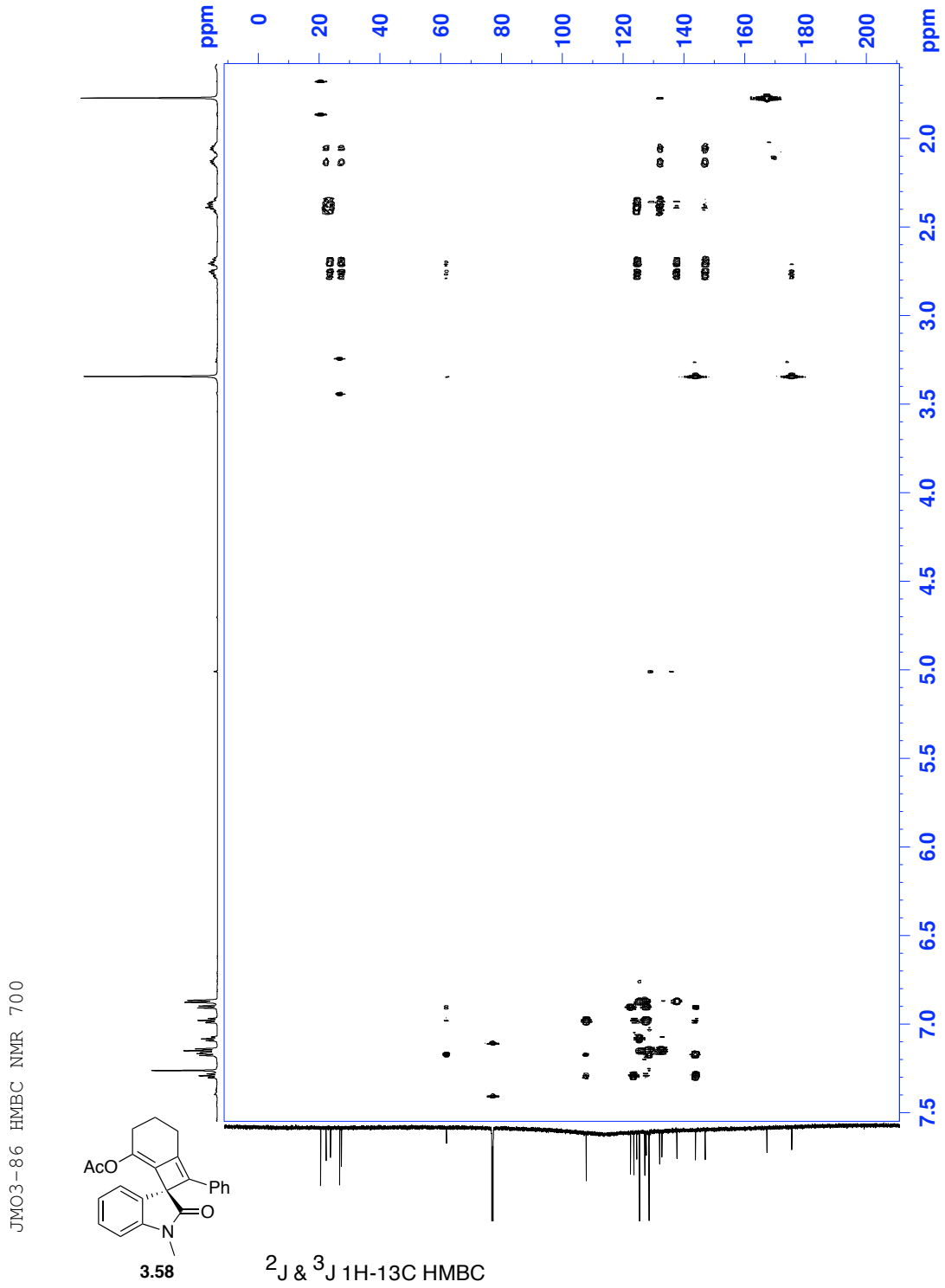

JMO3-86 1H NMR 700
7.300
7.289
7.278
7.260
7.175
7.164
7.159
7.148
7.137
7.091
7.081
7.071
6.990
6.979
6.968
6.908
6.897
6.877
6.865
3.343
2.779
2.776
2.767
2.762
2.754
2.751
2.743
2.715
2.705
2.697
2.691
2.681
2.673
2.413
2.398
2.389
2.381
2.377
2.370
2.367
2.359
2.343
2.152
2.143
2.134
2.125
2.115
2.106
2.072
2.070
2.062
2.054
2.051
2.043
1.771
7.3
7.2
7.1
7.0
6.9
ppm
2.8
2.7
2.6
2.5
2.4
2.3
2.2
ppm
AcO
N
O
Ph
3.58
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.04
0.99
1.99
0.95
0.97
0.94
1.85
2.71
1.00
1.00
2.09
1.07
1.11
2.71

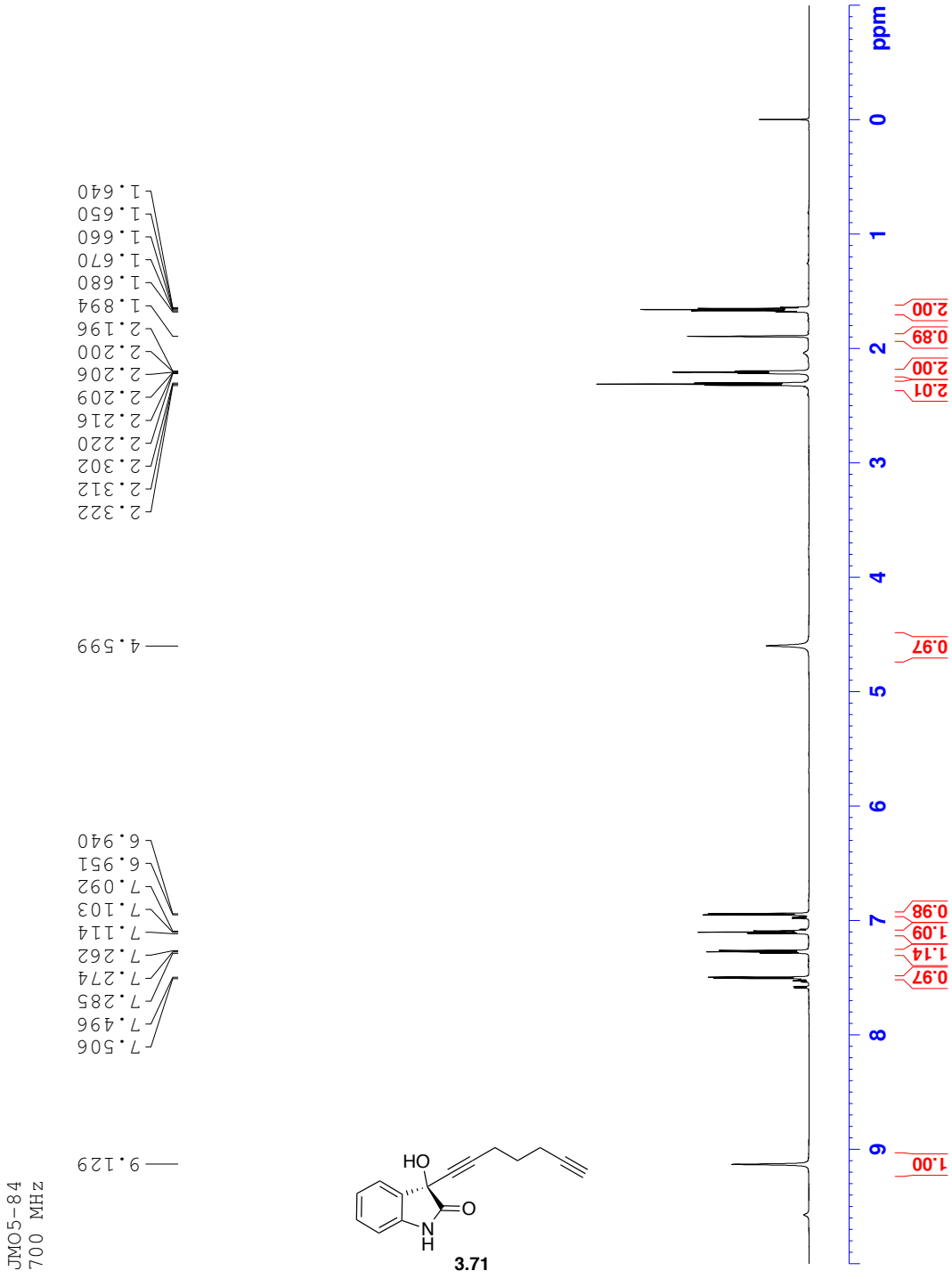

JMO3-86 DEPT 135 NMR 700
20.28
22.05
23.48
26.50
27.11
77.01
107.63
122.21
123.29
125.17
126.93
128.28
128.34
AcO
Ph
O
N
3.58
DEPT 135
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


JMO3-86 COSY NMR 500 MHz
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
AcO
Ph
O
N
3.58
1H-1H COSY

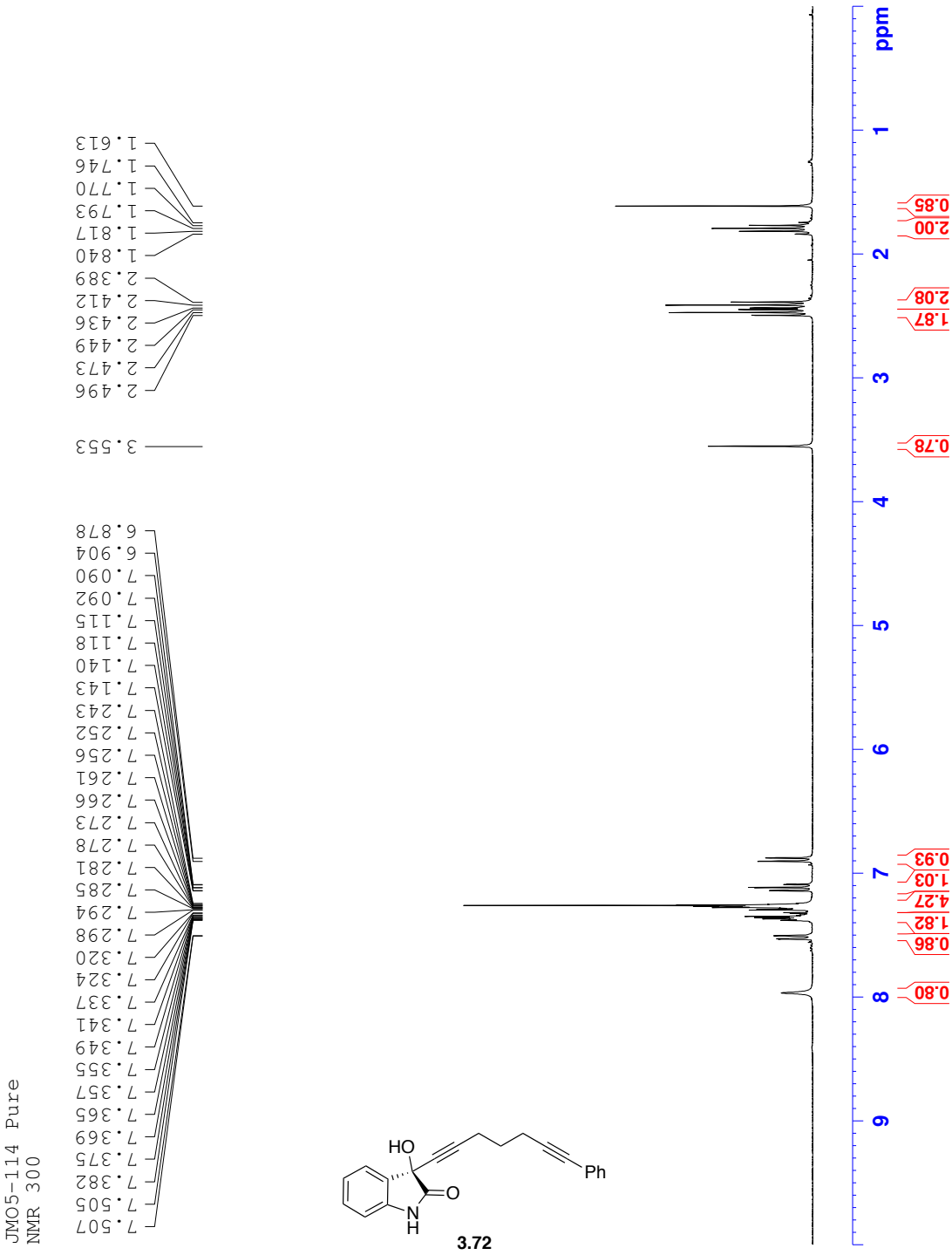

ppm
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
7
6
5
4
3
2
AcO
Ph
O
N
3.58

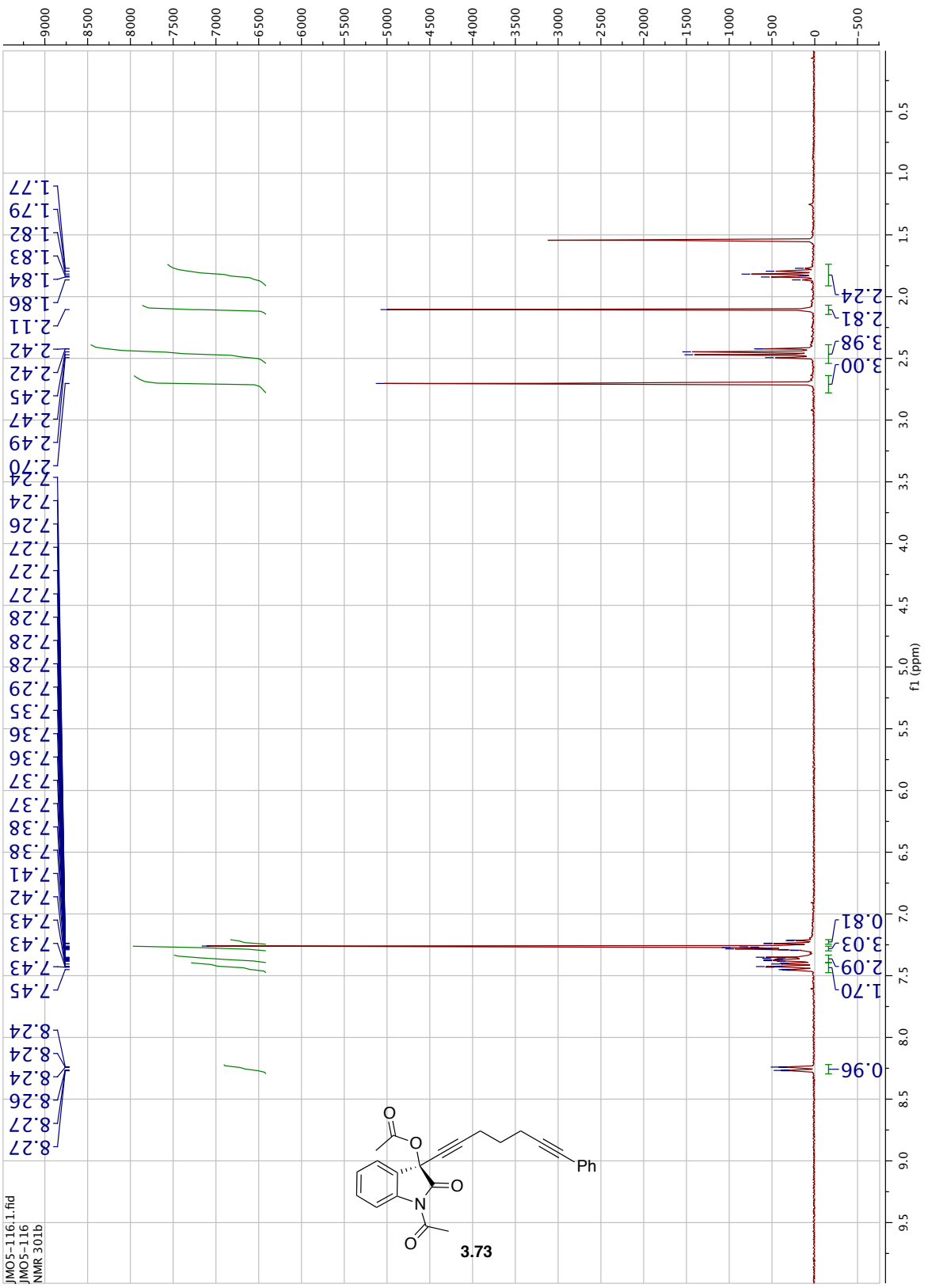
1H-13C HMQC

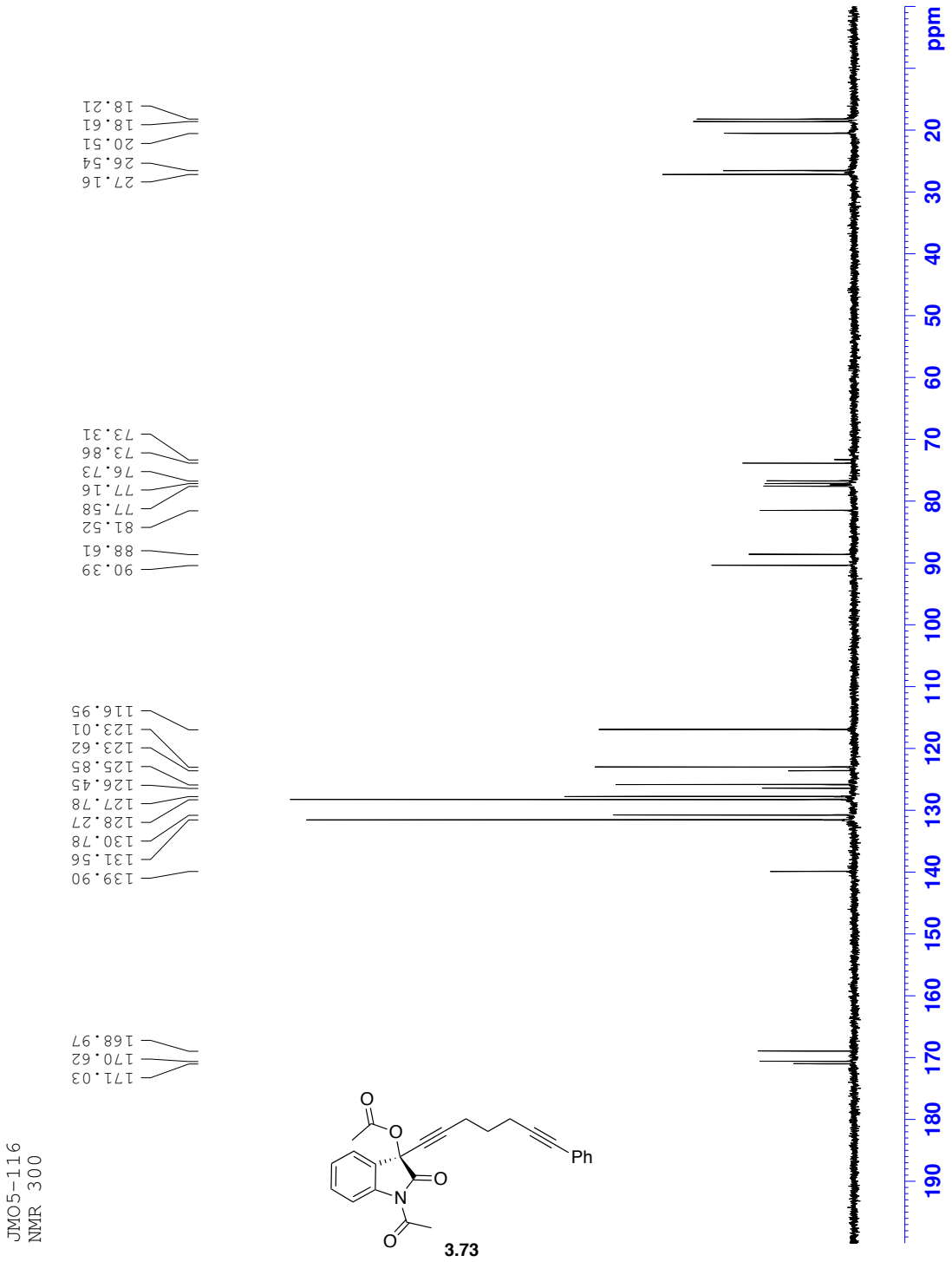

JMO3-86 HMBC NMR 700
ppm
0
20
40
60
80
100
120
140
160
180
200
ppm
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
AcO
Ph
O
N
3.58
2J & 3J 1H-13C HMBC

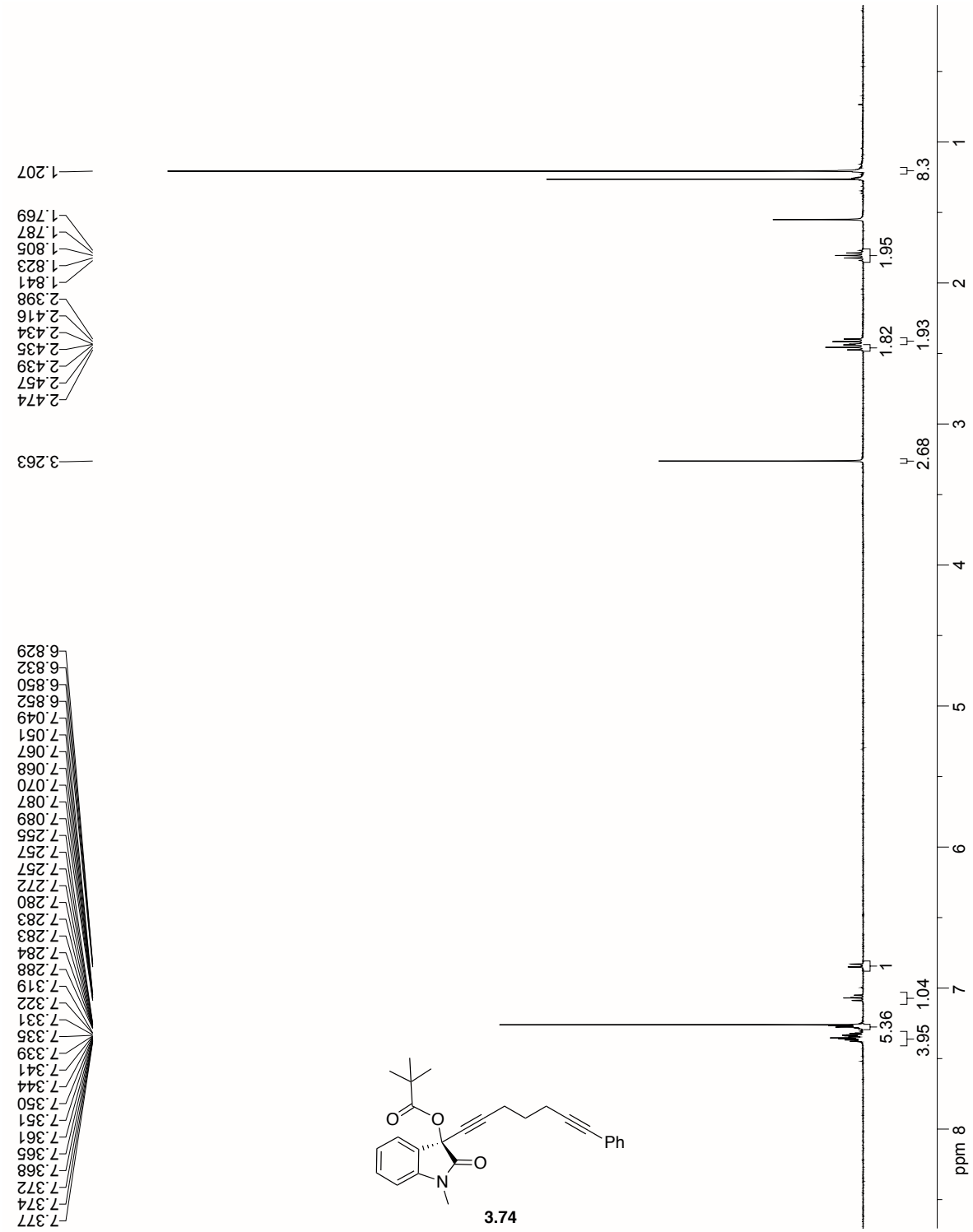

JMO5-84
700 MHz
9.129
7.506
7.496
7.285
7.274
7.262
7.114
7.103
7.092
6.951
6.940
4.599
2.322
2.312
2.302
2.220
2.216
2.209
2.206
2.200
2.196
1.894
1.680
1.670
1.660
1.650
1.640
HO
O
N
H
3.71
ppm
0
1
2
3
4
5
6
7
8
9
1.00
0.97
1.14
1.09
0.98
2.00
0.89
2.00
2.01
0.97

JMO5-84
700 MHz
177.26
140.16
130.35
129.98
124.82
123.78
110.96
87.02
83.32
77.30
69.71
69.06
27.04
17.88
17.51
HO
O
N
H
3.71
0 ppm


JMO5-114 Pure
NMR 300
7.507
7.505
7.382
7.375
7.369
7.365
7.357
7.355
7.349
7.341
7.337
7.324
7.320
7.298
7.294
7.285
7.281
7.278
7.273
7.266
7.261
7.256
7.252
7.243
7.143
7.140
7.118
7.115
7.092
7.090
6.904
6.878
3.553
2.496
2.473
2.449
2.436
2.412
2.389
1.840
1.817
1.793
1.770
1.746
1.613
ppm
1
2
3
4
5
6
7
8
9
0.85
2.00
2.08
1.87
0.78
0.93
1.03
4.27
1.82
0.86
0.80
HO
O
N
H
Ph
3.72

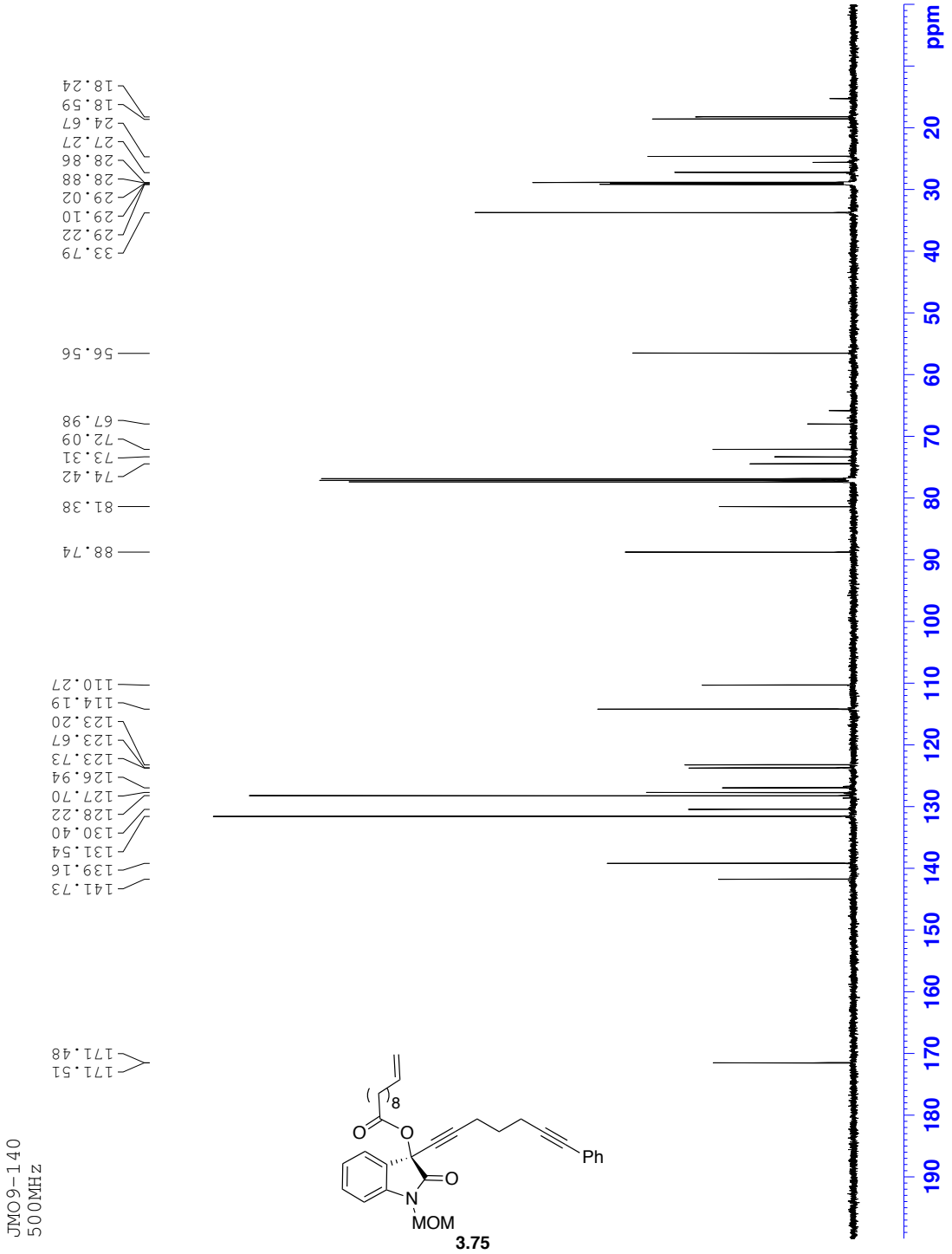

JMO5-116.1.fid
JMO5-116
NMR 301b
f1 (ppm)
Ph
3.73


JMO5-116
NMR 300
18.21
18.61
20.51
26.54
27.16
73.31
73.86
76.73
77.16
77.58
81.52
88.61
90.39
116.95
123.01
123.62
125.85
126.45
127.78
128.27
130.78
131.56
139.90
168.97
170.62
171.03
O
O
O
N
O
Ph
3.73
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

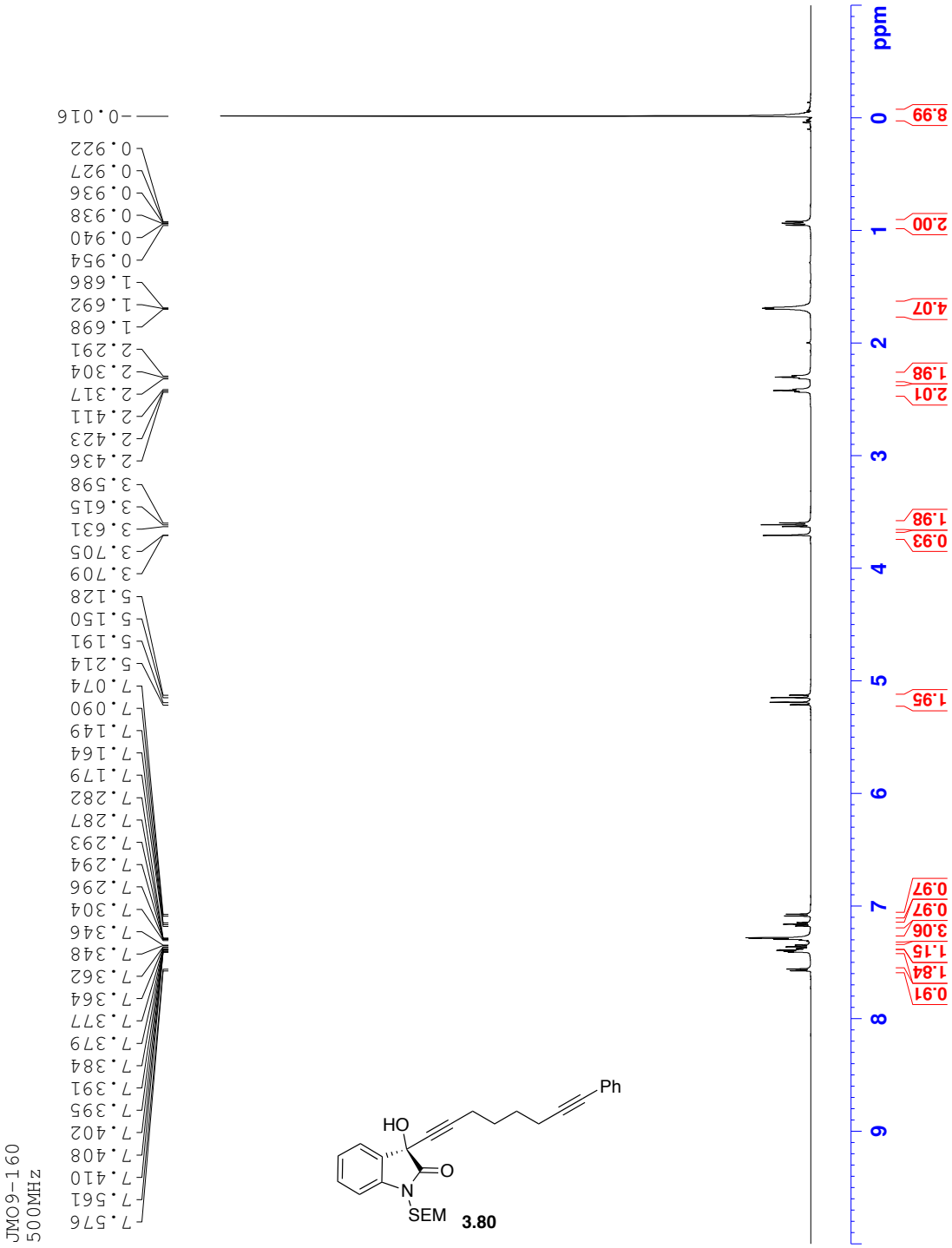

1.207
1.769
1.787
1.805
1.823
1.841
2.398
2.416
2.434
2.435
2.439
2.457
2.474
3.263
6.829
6.832
6.850
6.852
7.049
7.051
7.067
7.068
7.070
7.087
7.089
7.255
7.257
7.257
7.272
7.280
7.283
7.283
7.284
7.288
7.319
7.322
7.331
7.335
7.339
7.341
7.344
7.350
7.351
7.361
7.365
7.368
7.372
7.374
7.377
8.3
1.95
1.82
1.93
2.68
1
1.04
5.36
3.95
ppm
O
O
O
N
Ph

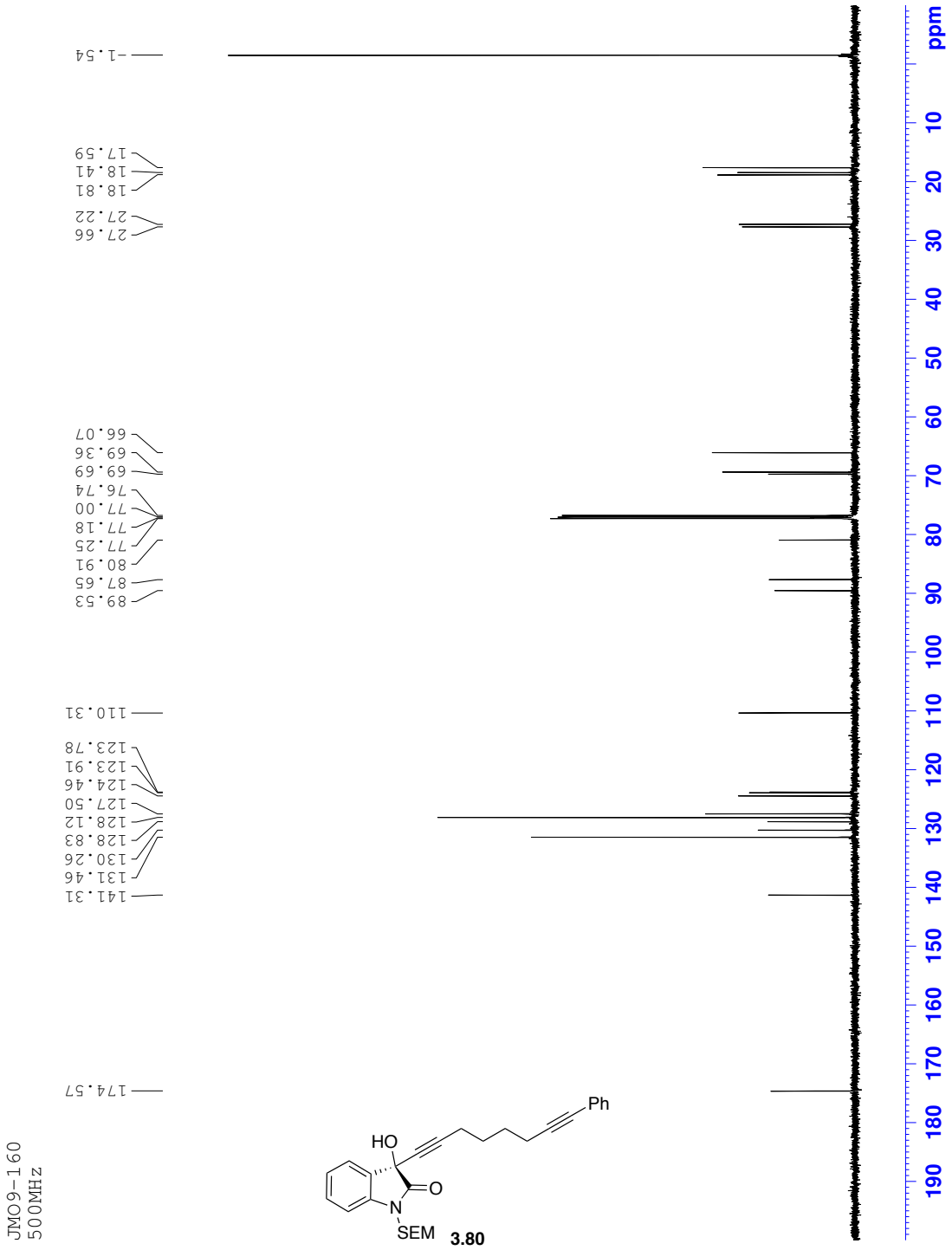
3.74

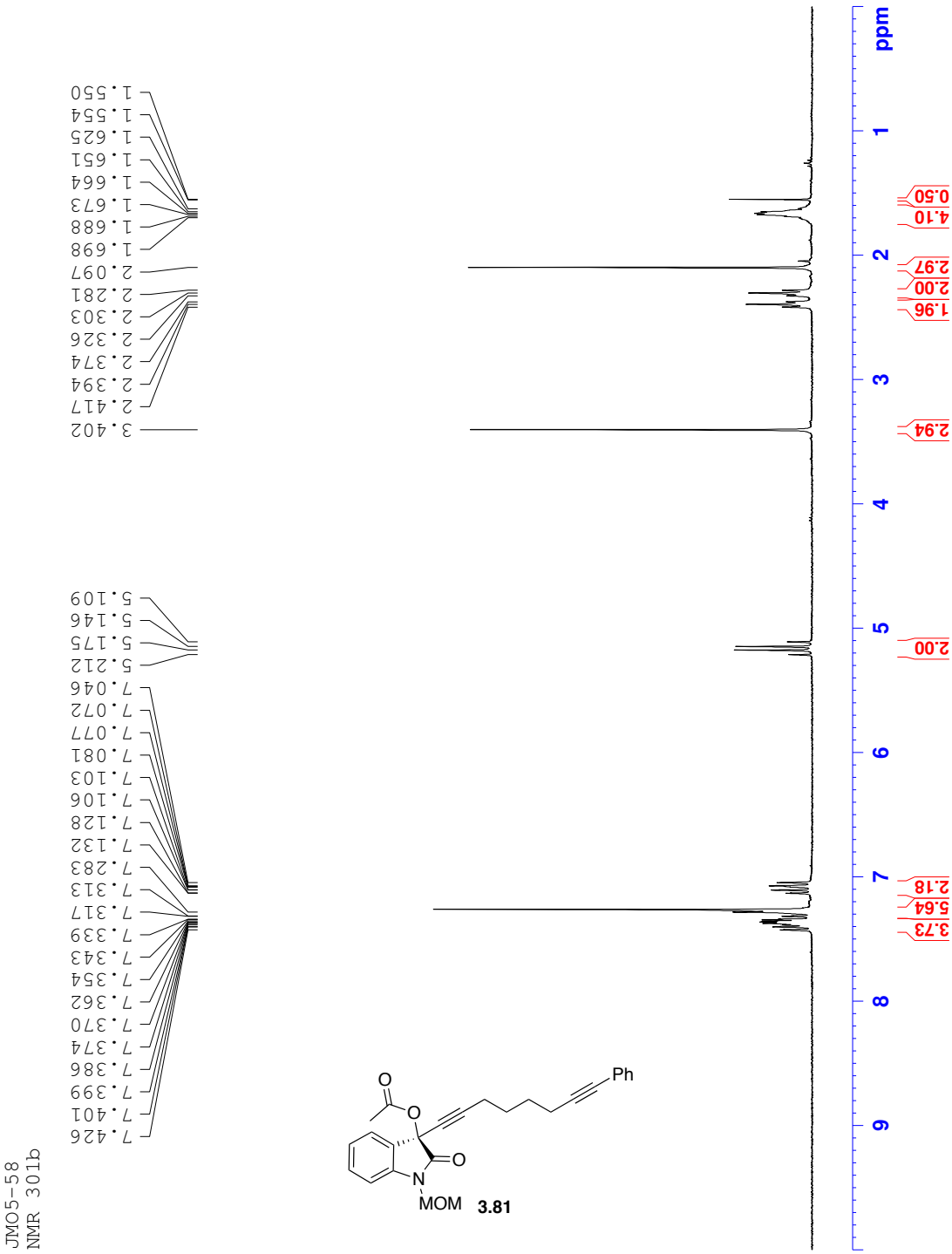
JMO9-140
500MHz
7.426
7.411
7.392
7.383
7.378
7.373
7.366
7.352
7.350
7.293
7.286
7.281
7.148
7.133
7.117
7.097
7.081
5.817
5.221
5.199
5.186
5.164
5.029
5.026
4.995
4.992
4.961
4.960
4.941
3.437
2.495
2.481
2.467
2.461
2.446
2.432
2.410
2.401
2.394
2.386
2.379
2.371
2.055
2.040
2.026
1.837
1.822
1.808
1.600
1.587
1.573
1.389
1.375
1.361
1.272
ppm
1
2
3
4
5
6
7
8
9
8.63
2.15
2.05
2.36
2.06
2.07
4.02
3.02
1.98
2.02
0.96
1.04
1.00
3.08
2.97
0.90
O
O
8
O
N
MOM
Ph
3.75

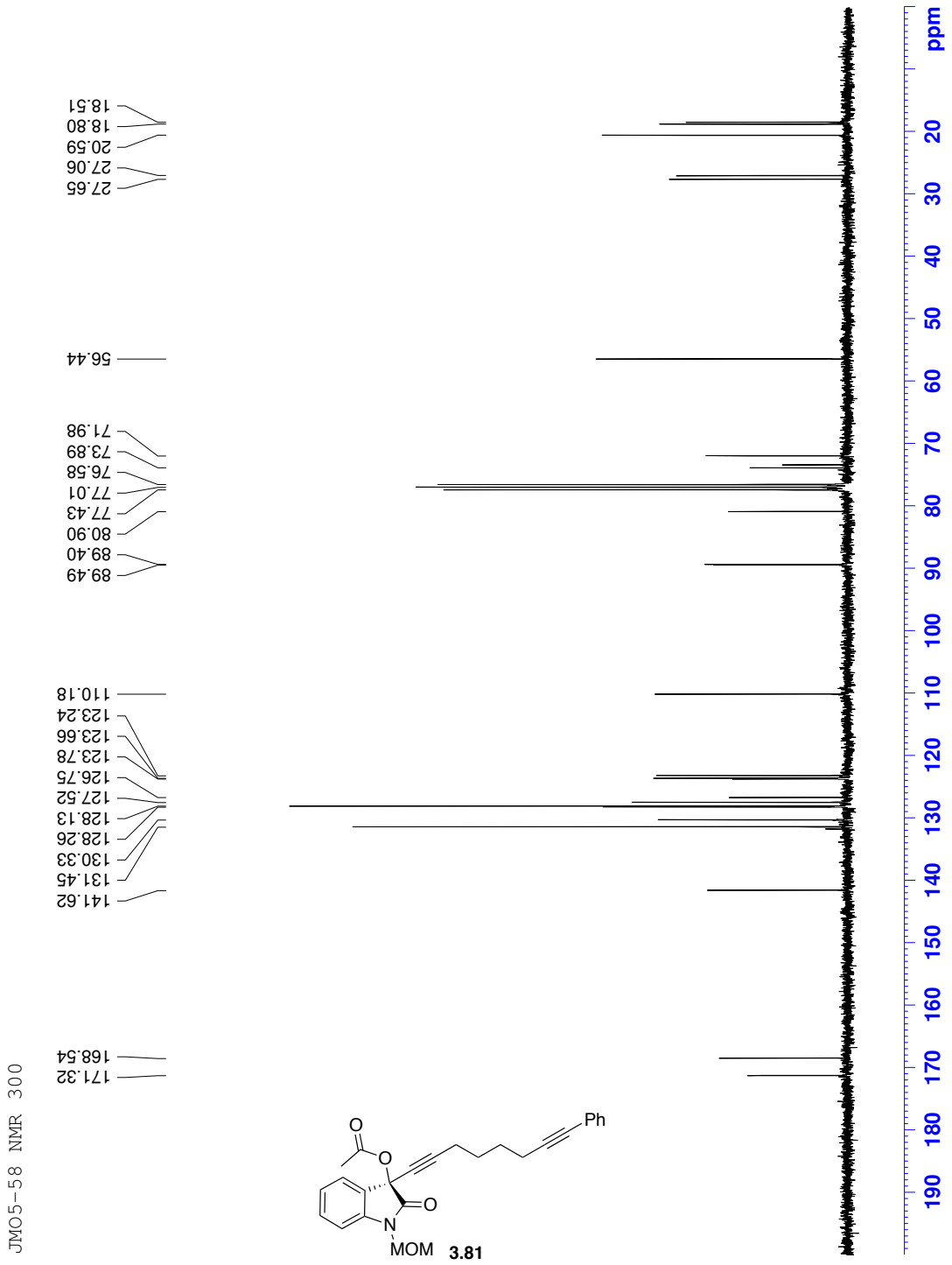

JM09-140
500MHz
171.51
171.48
141.73
139.16
131.54
130.40
128.22
127.70
126.94
123.73
123.67
123.20
114.19
110.27
88.74
81.38
74.42
73.31
72.09
67.98
56.56
33.79
29.22
29.10
29.02
28.88
28.86
27.27
24.67
18.59
18.24
ppm
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
8
O
O
O
N
MOM
Ph

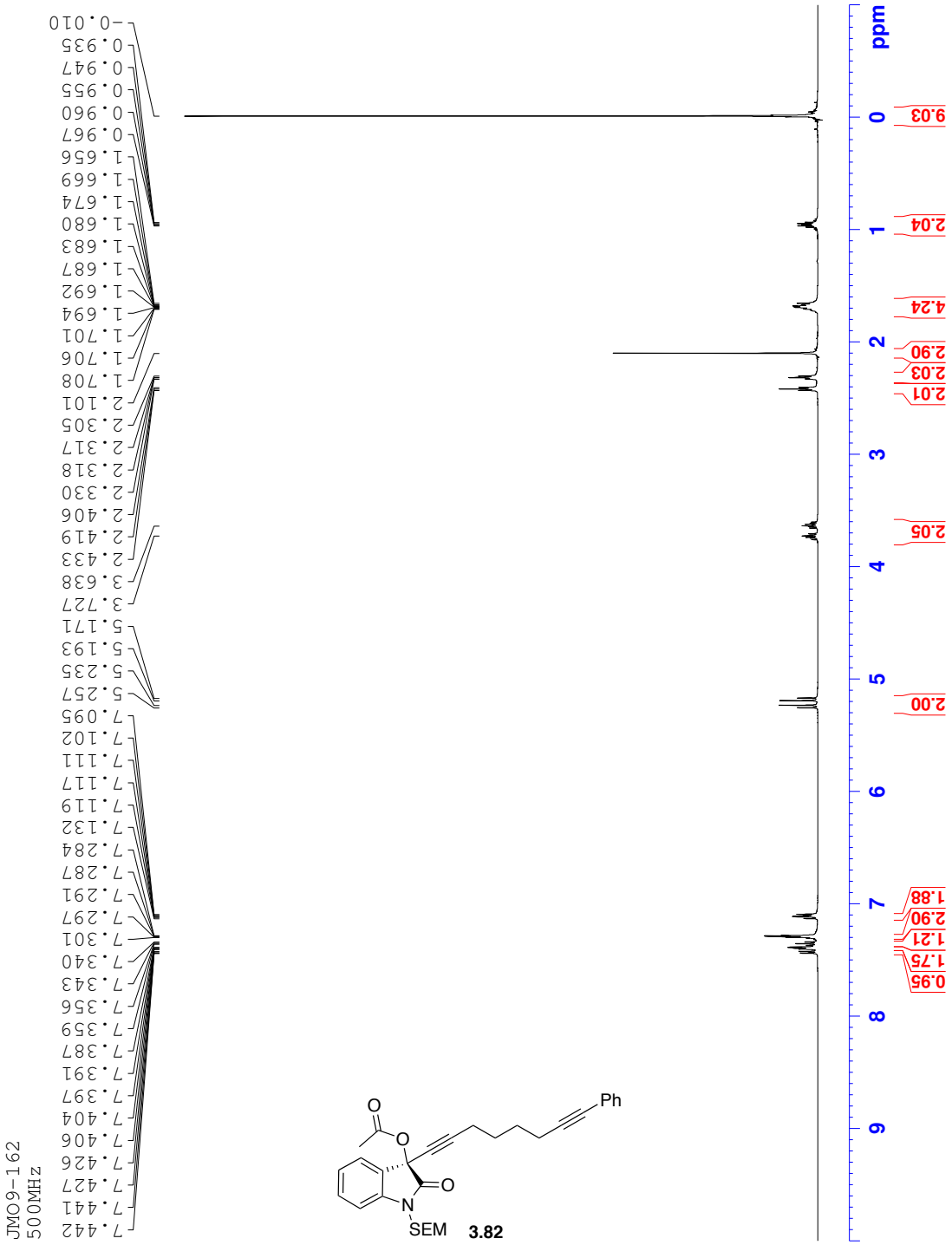
3.75


JMO9-160
500MHz
0.016
0.922
0.927
0.936
0.938
0.940
0.954
1.686
1.692
1.698
2.291
2.304
2.317
2.411
2.423
2.436
3.598
3.615
3.631
3.705
3.709
5.128
5.150
5.191
5.214
7.074
7.090
7.149
7.164
7.179
7.282
7.287
7.293
7.294
7.296
7.304
7.346
7.348
7.362
7.364
7.377
7.379
7.384
7.391
7.395
7.402
7.408
7.410
7.561
7.576
ppm
0
1
2
3
4
5
6
7
8
9
8.99
2.00
4.07
1.98
2.01
1.98
0.93
1.95
0.91
1.84
1.15
3.06
0.97
0.97
HO
O
N
SEM
Ph
3.80


-1.54
17.59
18.41
18.81
27.22
27.66
66.07
69.36
69.69
76.74
77.00
77.18
77.25
80.91
87.65
89.53
110.31
123.78
123.91
124.46
127.50
128.12
128.83
130.26
131.46
141.31
174.57
JMO9-160
500MHz
HO
O
N
SEM
Ph
3.80
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


JMO5-58
NMR 301b
7.426
7.401
7.399
7.386
7.374
7.370
7.362
7.354
7.343
7.339
7.317
7.313
7.283
7.132
7.128
7.106
7.103
7.081
7.077
7.072
7.046
5.212
5.175
5.146
5.109
3.402
2.417
2.394
2.374
2.326
2.303
2.281
2.097
1.698
1.688
1.673
1.664
1.651
1.625
1.554
1.550
ppm
1
2
3
4
5
6
7
8
9
0.50
4.10
2.97
2.00
1.96
2.94
2.00
2.18
5.64
3.73
O
O
O
N
MOM
Ph
3.81


JMO5-58 NMR 300
168.54
171.32
141.62
131.45
130.33
128.26
128.13
127.52
126.75
123.78
123.66
123.24
110.18
89.49
89.40
80.90
77.43
77.01
76.58
73.89
71.98
56.44
27.65
27.06
20.59
18.80
18.51
ppm
O
O
O
N
MOM
Ph
3.81


JM09-162
500MHz
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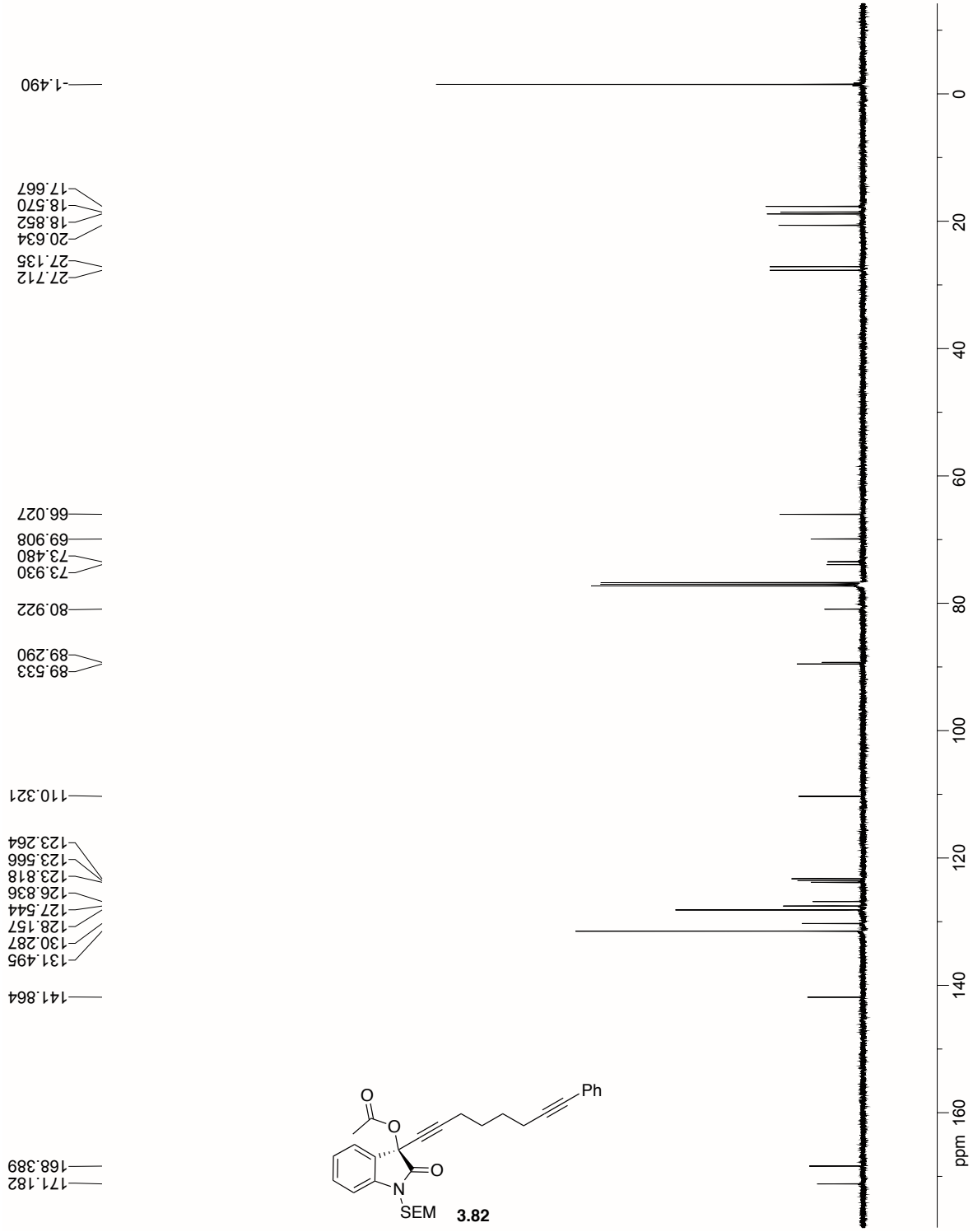
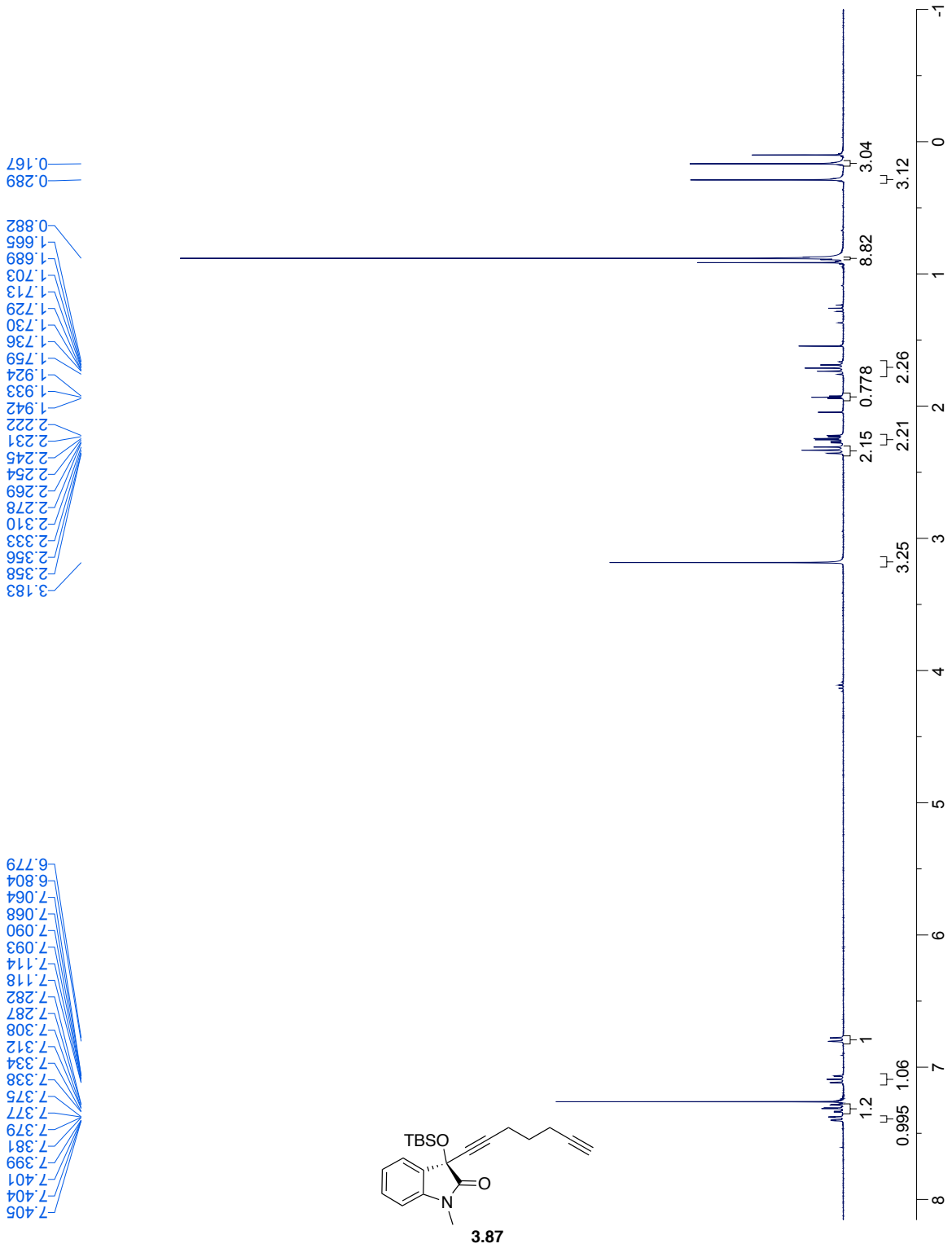
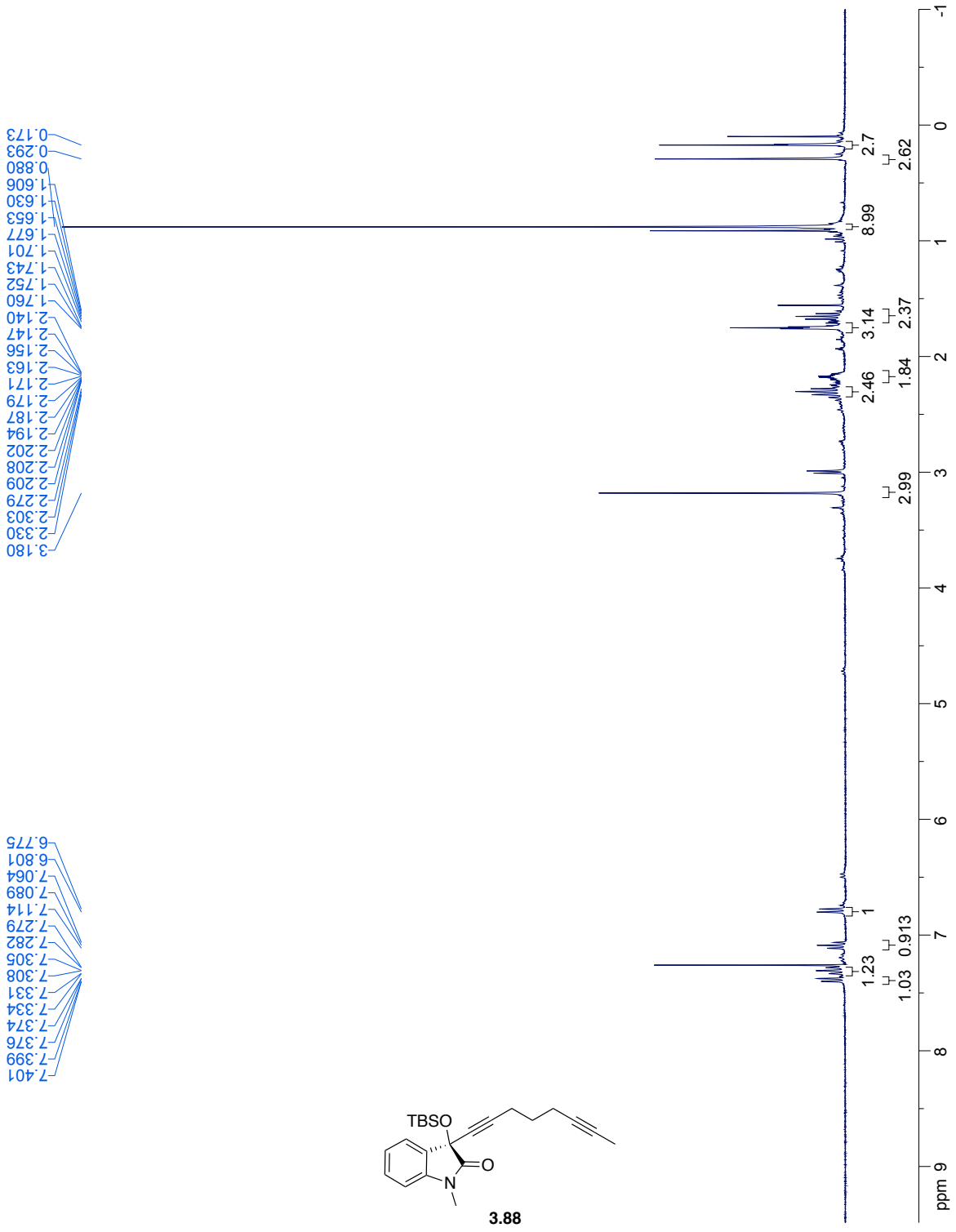
7.441
7.427
7.426
7.406
7.404
7.397
7.391
7.387
7.359
7.356
7.343
7.340
7.301
7.297
7.291
7.287
7.284
7.132
7.119
7.117
7.111
7.102
7.095
5.257
5.235
5.193
5.171
3.727
3.638
2.433
2.419
2.406
2.330
2.318
2.317
2.305
2.101
1.708
1.706
1.701
1.694
1.692
1.687
1.683
1.680
1.674
1.669
1.656
0.967
0.960
0.955
0.947
0.935
-0.010
ppm
0
1
2
3
4
5
6
7
8
9
9.03
2.04
4.24
2.90
2.03
2.01
2.05
2.00
0.95
1.75
1.21
2.90
1.88
O
O
O
N
SEM
Ph
3.82


-1.490
17.667
18.570
18.852
20.634
27.135
27.712
66.027
69.908
73.480
73.930
80.922
89.290
89.533
110.321
123.264
123.566
123.818
126.836
127.544
128.157
130.287
131.495
141.864
168.389
171.182
ppm
0
20
40
60
80
100
120
140
160
O
O
O
N
SEM
Ph
3.82


0.167
0.289
0.882
1.665
1.689
1.703
1.713
1.729
1.730
1.736
1.759
1.924
1.933
1.942
2.222
2.231
2.245
2.254
2.269
2.278
2.310
2.333
2.356
2.358
3.183
6.779
6.804
7.064
7.068
7.090
7.093
7.114
7.118
7.282
7.287
7.308
7.312
7.334
7.338
7.375
7.377
7.379
7.381
7.399
7.401
7.404
7.405
TBSO
O
N
3.87
3.04
3.12
8.82
0.778
2.26
2.15
2.21
3.25
1
1.06
1.2
0.995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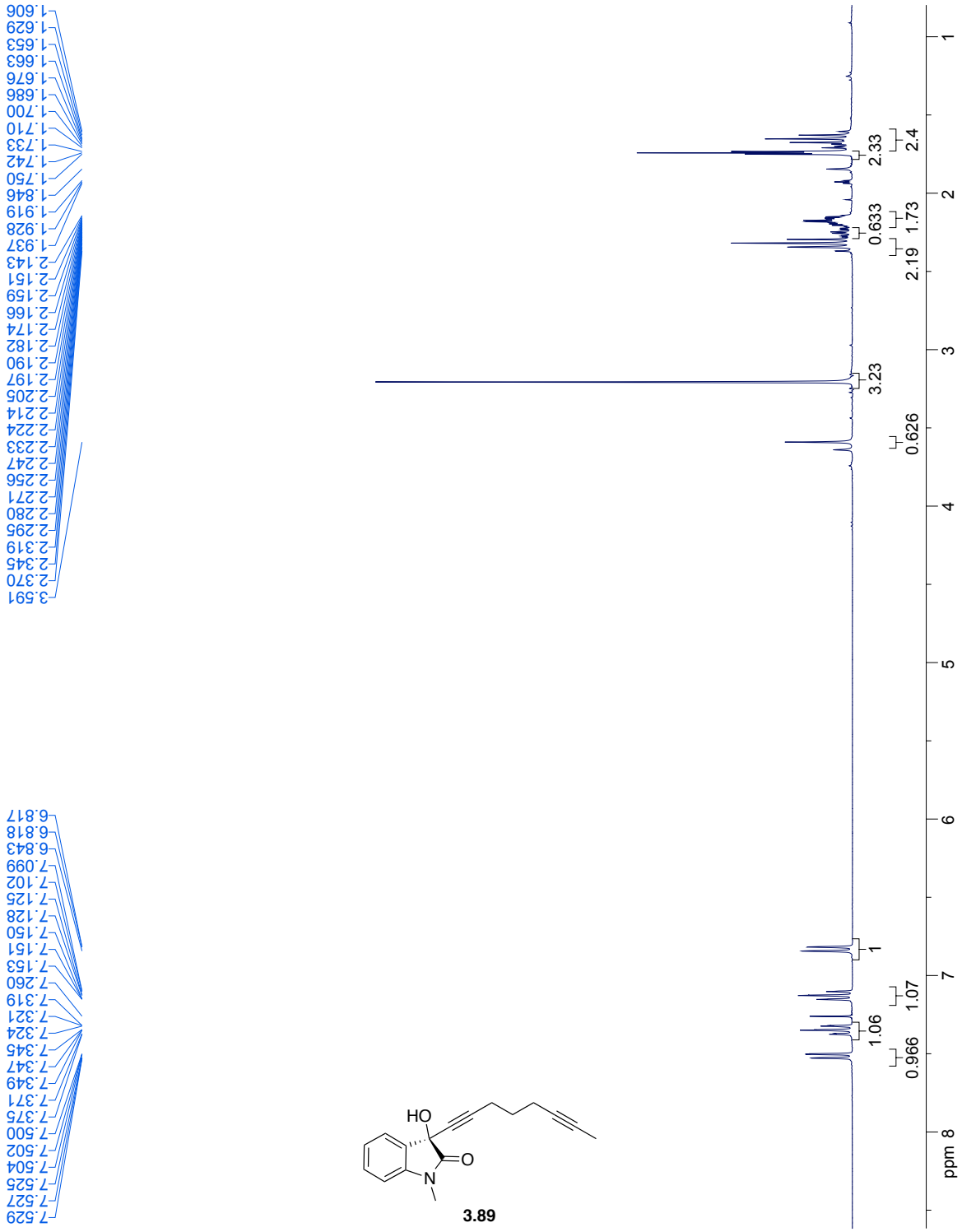
0.293
0.880
1.606
1.630
1.653
1.677
1.701
1.743
1.752
1.760
2.140
2.147
2.156
2.163
2.171
2.179
2.187
2.194
2.202
2.208
2.209
2.279
2.303
2.330
3.180
6.775
6.801
7.064
7.089
7.114
7.279
7.282
7.305
7.308
7.331
7.334
7.374
7.376
7.399
7.401
2.7
2.62
8.99
3.14
2.37
2.46
1.84
2.99
1
1.23
1.03
0.913
TBSO
O
N
3.88
ppm


1.606
1.629
1.653
1.663
1.676
1.686
1.700
1.710
1.733
1.742
1.750
1.846
1.919
1.928
1.937
2.143
2.151
2.159
2.166
2.174
2.182
2.190
2.197
2.205
2.214
2.224
2.233
2.247
2.256
2.271
2.280
2.295
2.319
2.345
2.370
3.591
6.817
6.818
6.843
7.099
7.102
7.125
7.128
7.150
7.151
7.153
7.260
7.319
7.321
7.324
7.345
7.347
7.349
7.371
7.375
7.500
7.502
7.504
7.525
7.527
7.529
HO
O
N
3.89
2.33
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0.633
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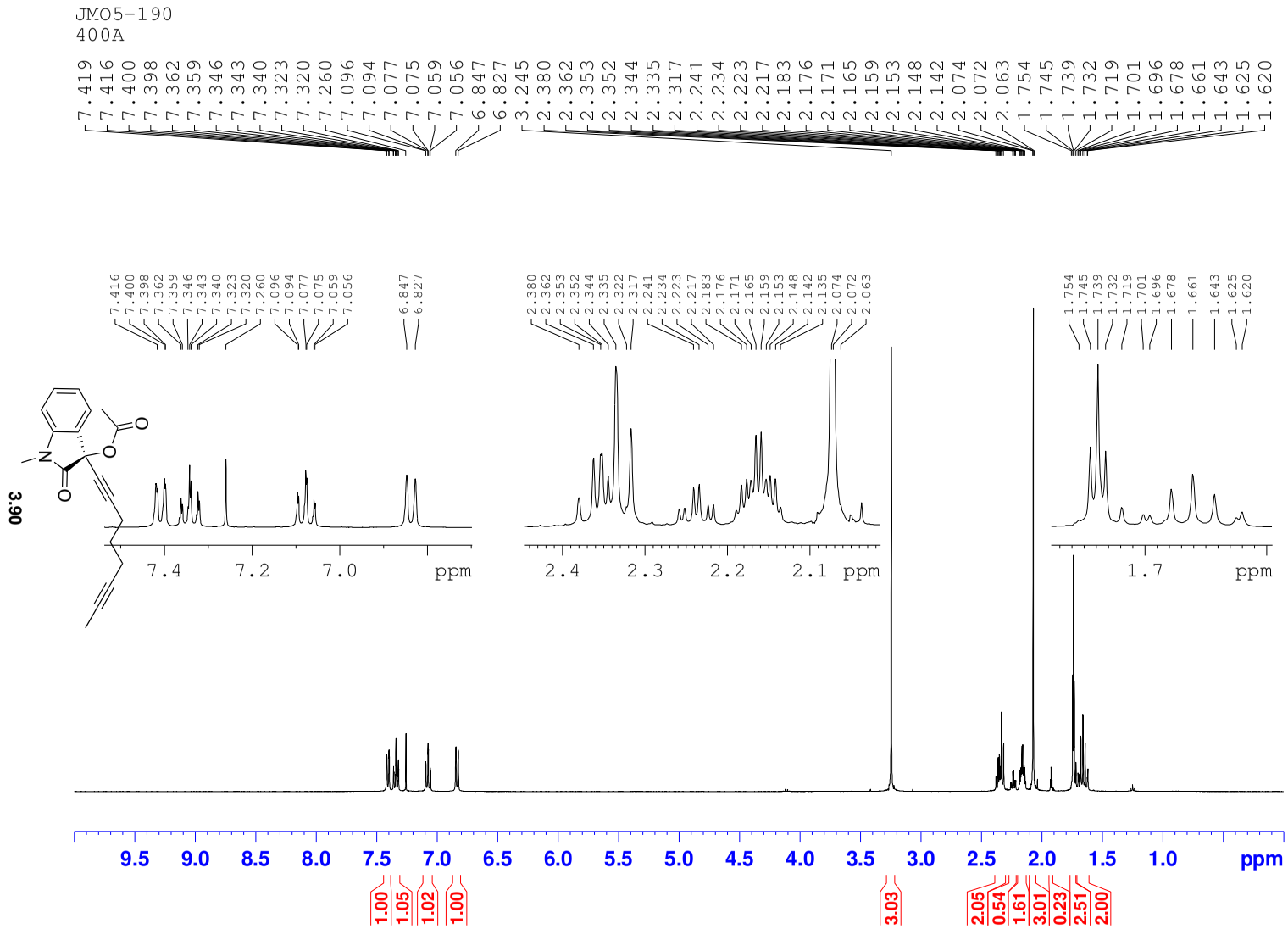
1
1.07
1.06
0.966
ppm 8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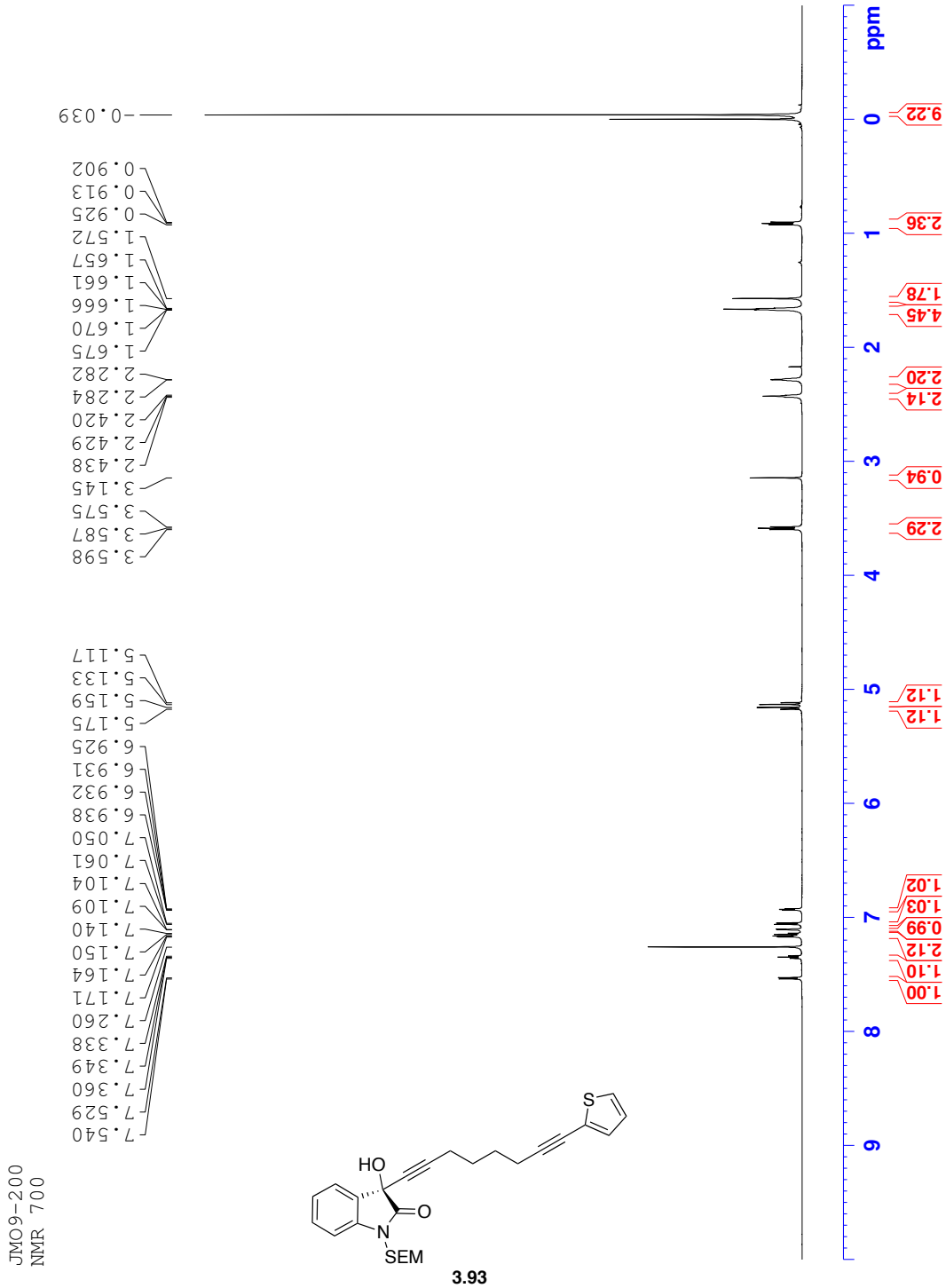
400A
7.419 7.416 7.400 7.398 7.362 7.359 7.346 7.343 7.340 7.323 7.320 7.260 7.096 7.094 7.077 7.075 7.059 7.056 6.847 6.827
3.245 2.380 2.362 2.353 2.352 2.344 2.335 2.317 2.241 2.234 2.223 2.217 2.183 2.176 2.171 2.165 2.159 2.153 2.148 2.142 2.074 2.072 2.063
1.754 1.745 1.739 1.732 1.719 1.701 1.696 1.678 1.661 1.643 1.625 1.620
3.90
7.4 7.2 7.0 ppm
2.4 2.3 2.2 2.1 ppm
1.7 ppm
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00 1.05 1.02 1.00
3.03
2.05 0.54 1.61 3.01 0.23 2.51 2.00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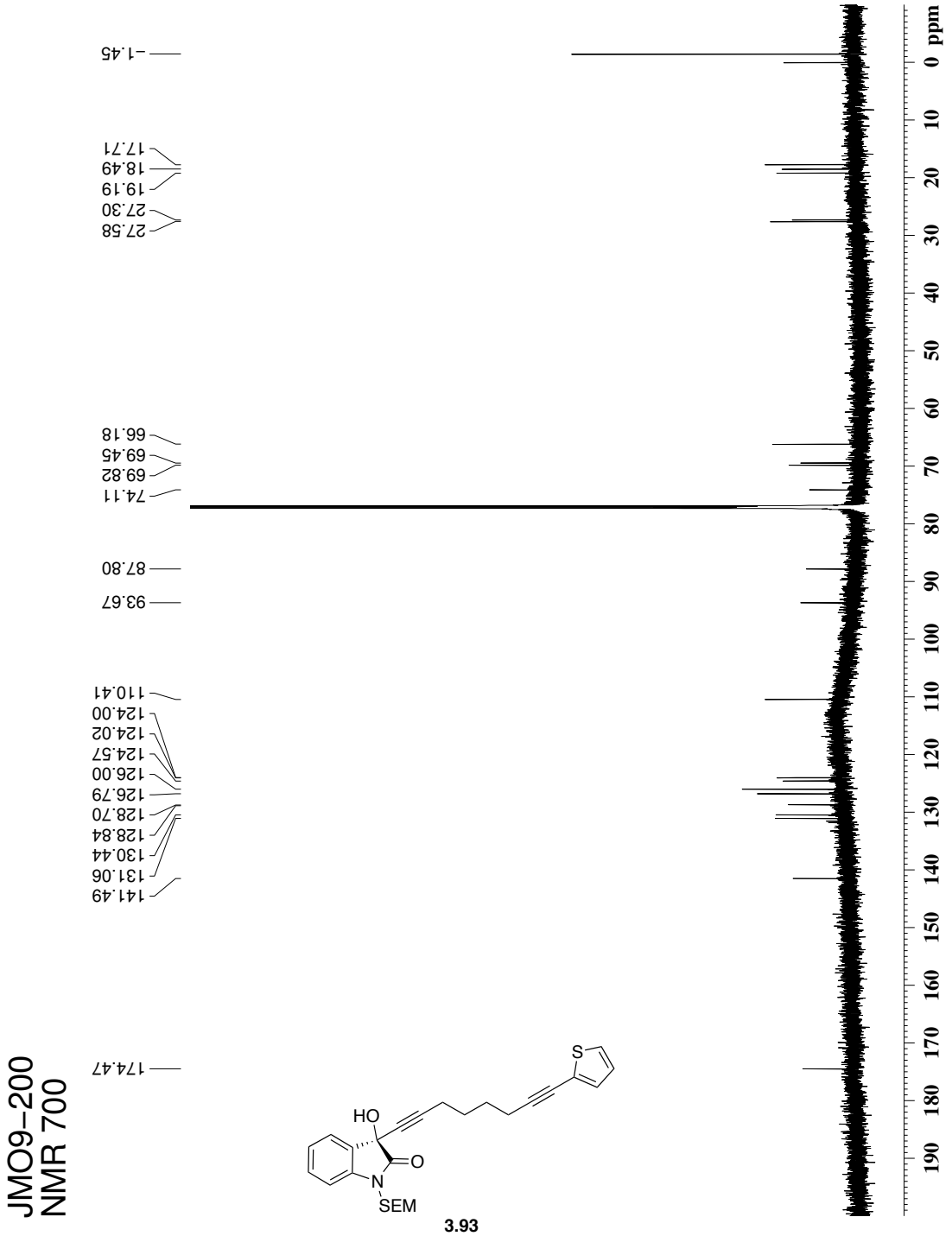
0.913
0.925
1.572
1.657
1.661
1.666
1.670
1.675
2.282
2.284
2.420
2.429
2.438
3.145
3.575
3.587
3.598
5.117
5.133
5.159
5.175
6.925
6.931
6.932
6.938
7.050
7.061
7.104
7.109
7.140
7.150
7.164
7.171
7.260
7.338
7.349
7.360
7.529
7.540
ppm
9.22
2.36
1.78
4.45
2.20
2.14
0.94
2.29
1.12
1.12
1.02
1.03
0.99
2.12
1.10
1.00
HO
O
N
SEM
S
3.93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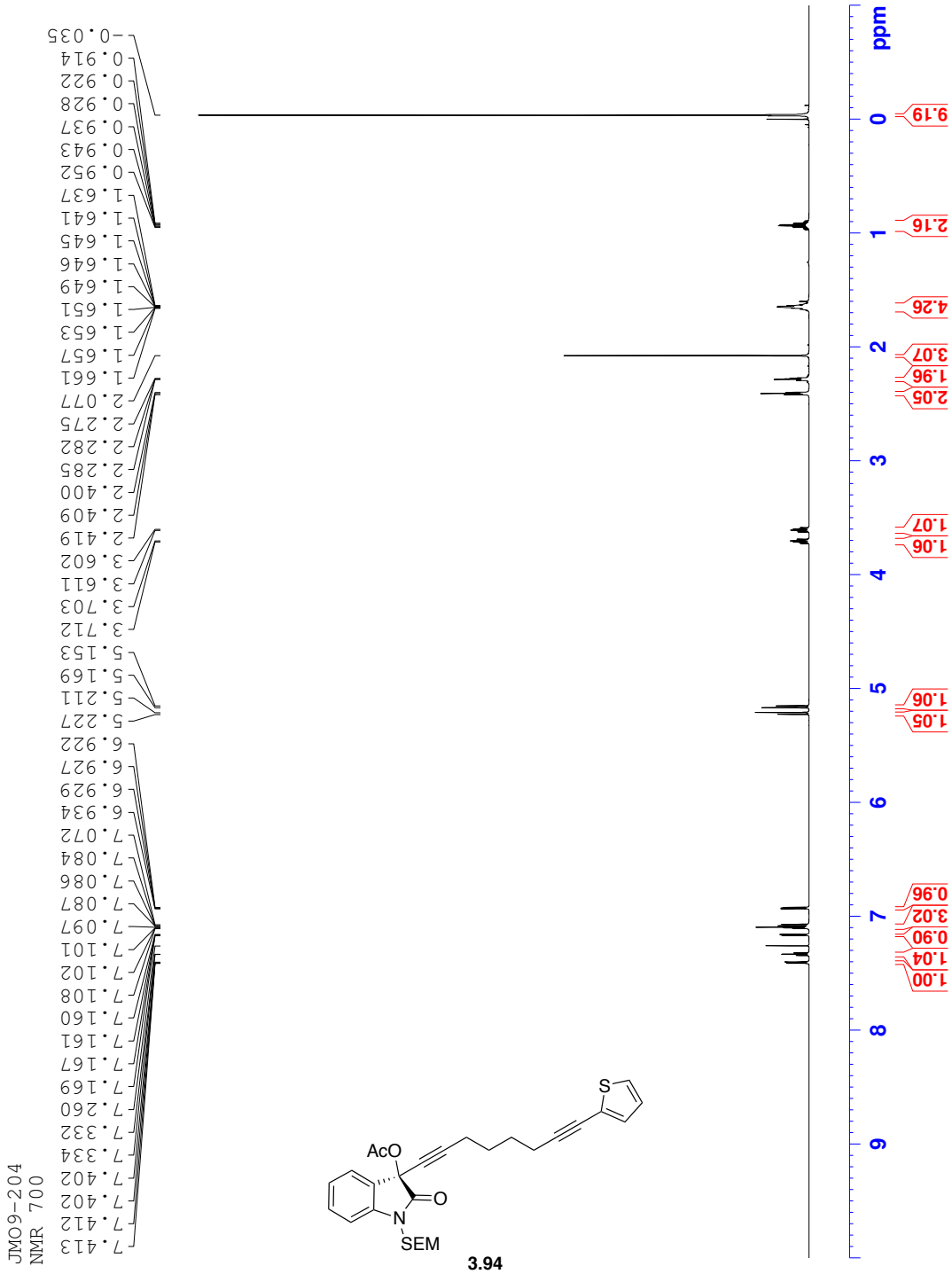
17.71
18.49
19.19
27.30
27.58
66.18
69.45
69.82
74.11
87.80
93.67
110.41
124.00
124.02
124.57
126.00
126.79
128.70
128.84
130.44
131.06
141.49
174.47
HO
O
N
SEM
S
3.93
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190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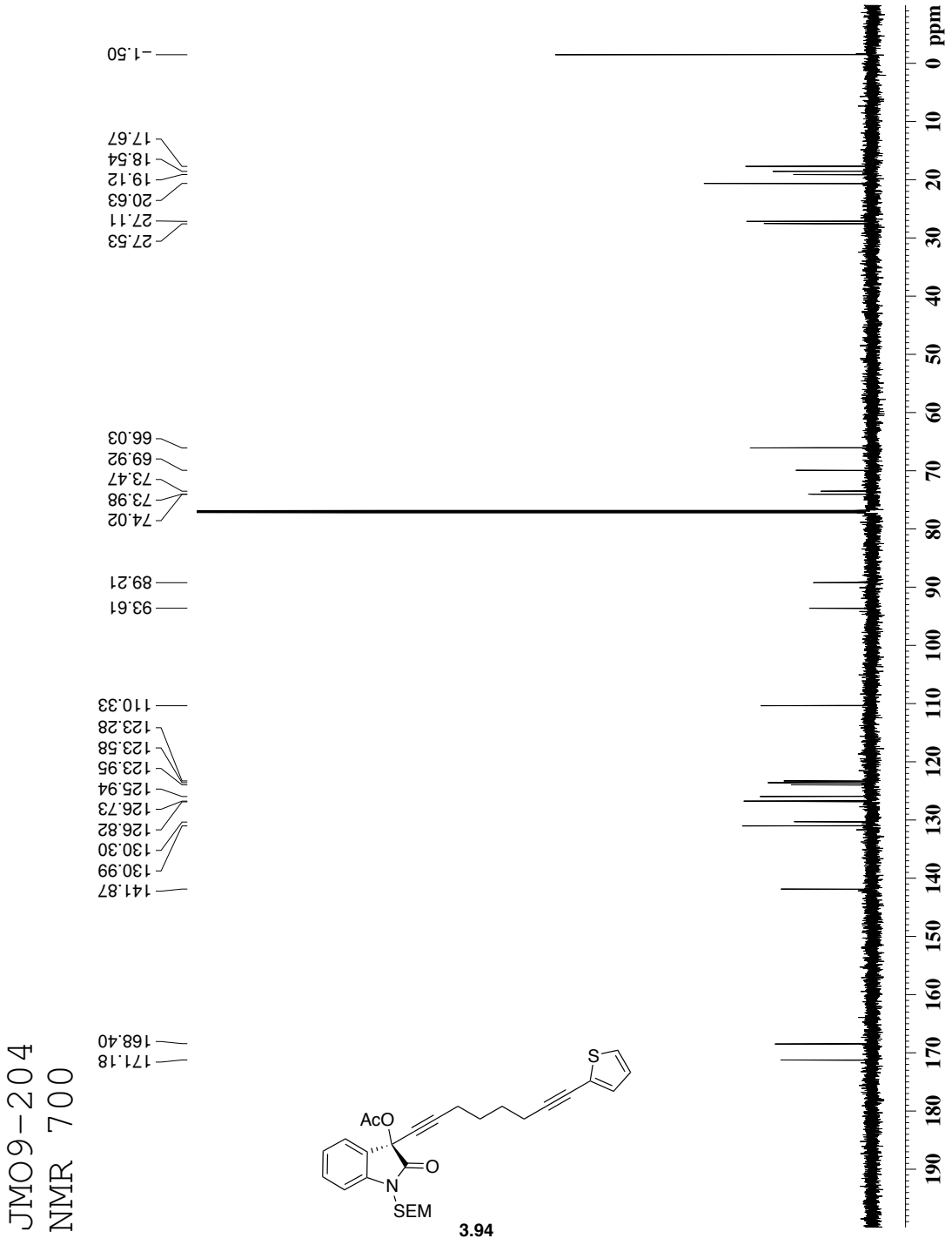
AcO
O
N
SEM
S
3.94
ppm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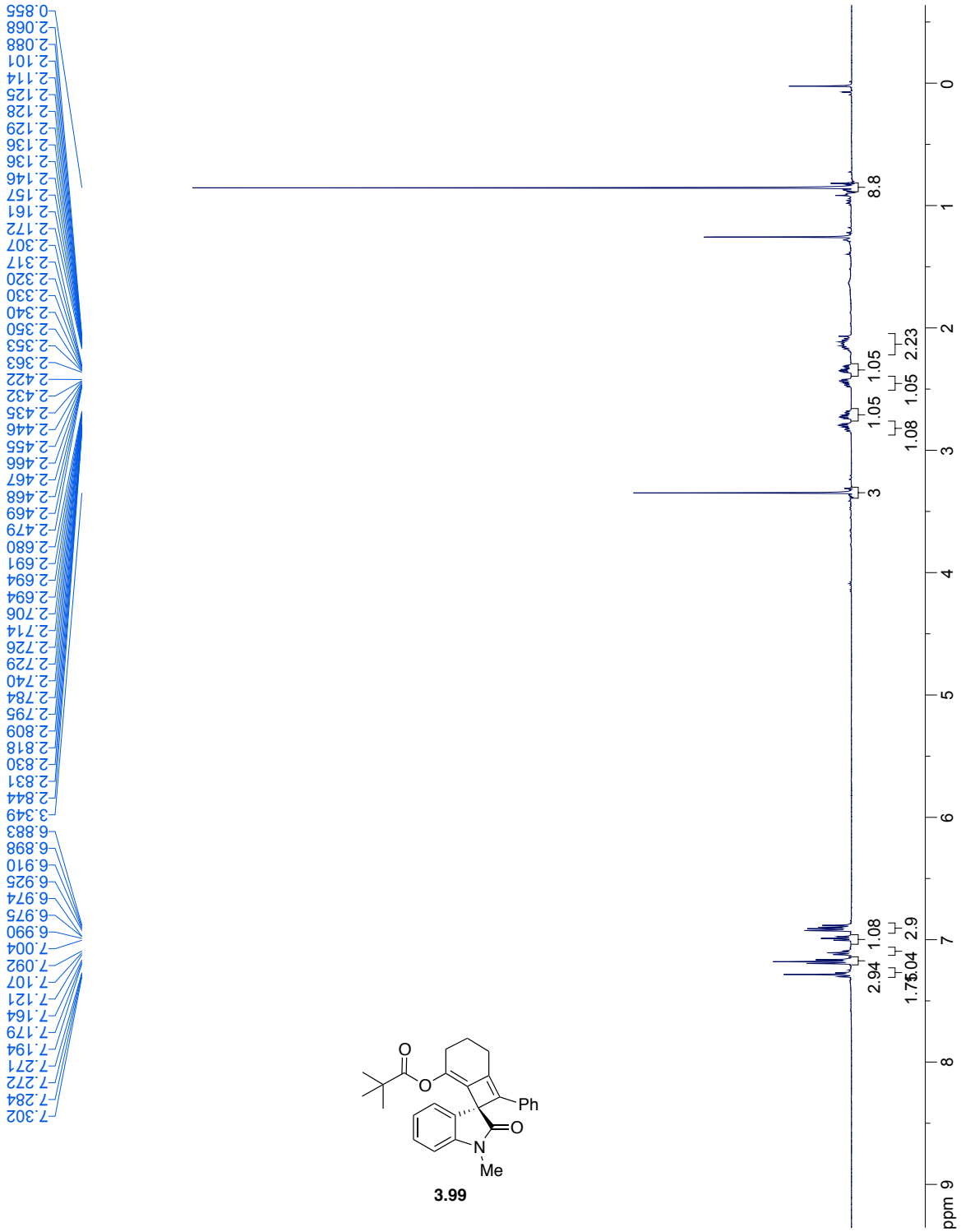
18.54
19.12
20.63
27.11
27.53
66.03
69.92
73.47
73.98
74.02
89.21
93.61
110.33
123.28
123.58
123.95
125.94
126.73
126.82
130.30
130.99
141.87
168.40
171.18
AcO
O
N
SEM
S
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190

3.94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2.088
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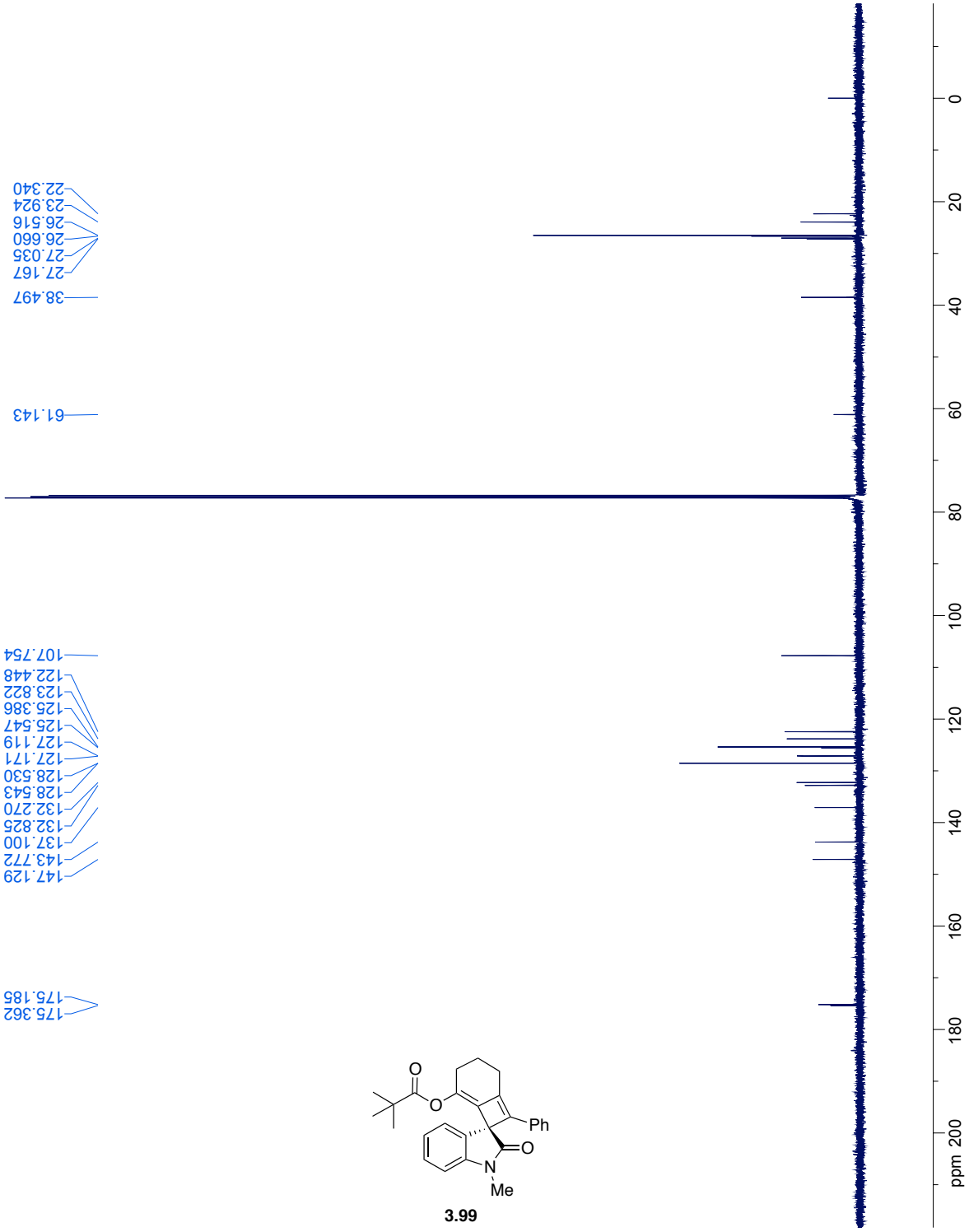
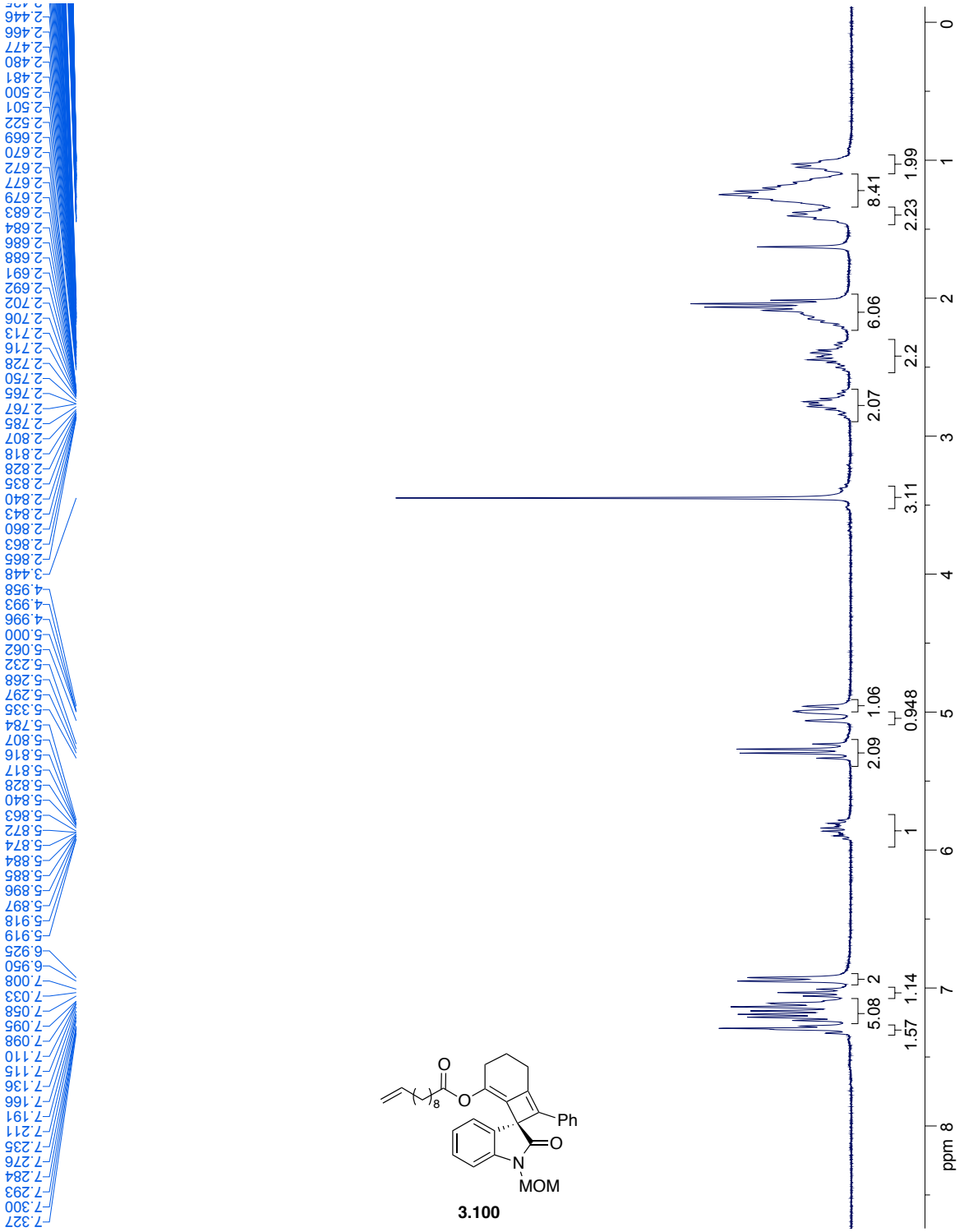
2.125
2.128
2.129
2.136
2.136
2.146
2.157
2.161
2.172
2.307
2.317
2.320
2.330
2.340
2.350
2.353
2.363
2.422
2.432
2.435
2.446
2.455
2.466
2.467
2.468
2.469
2.479
2.680
2.691
2.694
2.694
2.706
2.714
2.726
2.729
2.740
2.784
2.795
2.809
2.818
2.830
2.831
2.844
3.349
6.883
6.898
6.910
6.925
6.974
6.975
6.990
7.004
7.092
7.107
7.121
7.164
7.179
7.194
7.271
7.272
7.284
7.302
8.8
3
1.08
1.05
1.05
1.05
2.23
2.94
1.08
1.75
1.04
2.9
ppm 9
8
7
6
5
4
3
2
1
0
O
O
Ph
O
N
Me

3.99


22.340
23.924
26.516
26.660
27.035
27.167
38.497
61.143
107.754
122.448
123.822
125.386
125.547
127.119
127.171
128.530
128.543
132.270
132.825
137.100
143.772
147.129
175.362
175.185
0
20
40
60
80
100
120
140
160
180
200
ppm
O
O
Ph
O
N
Me

3.99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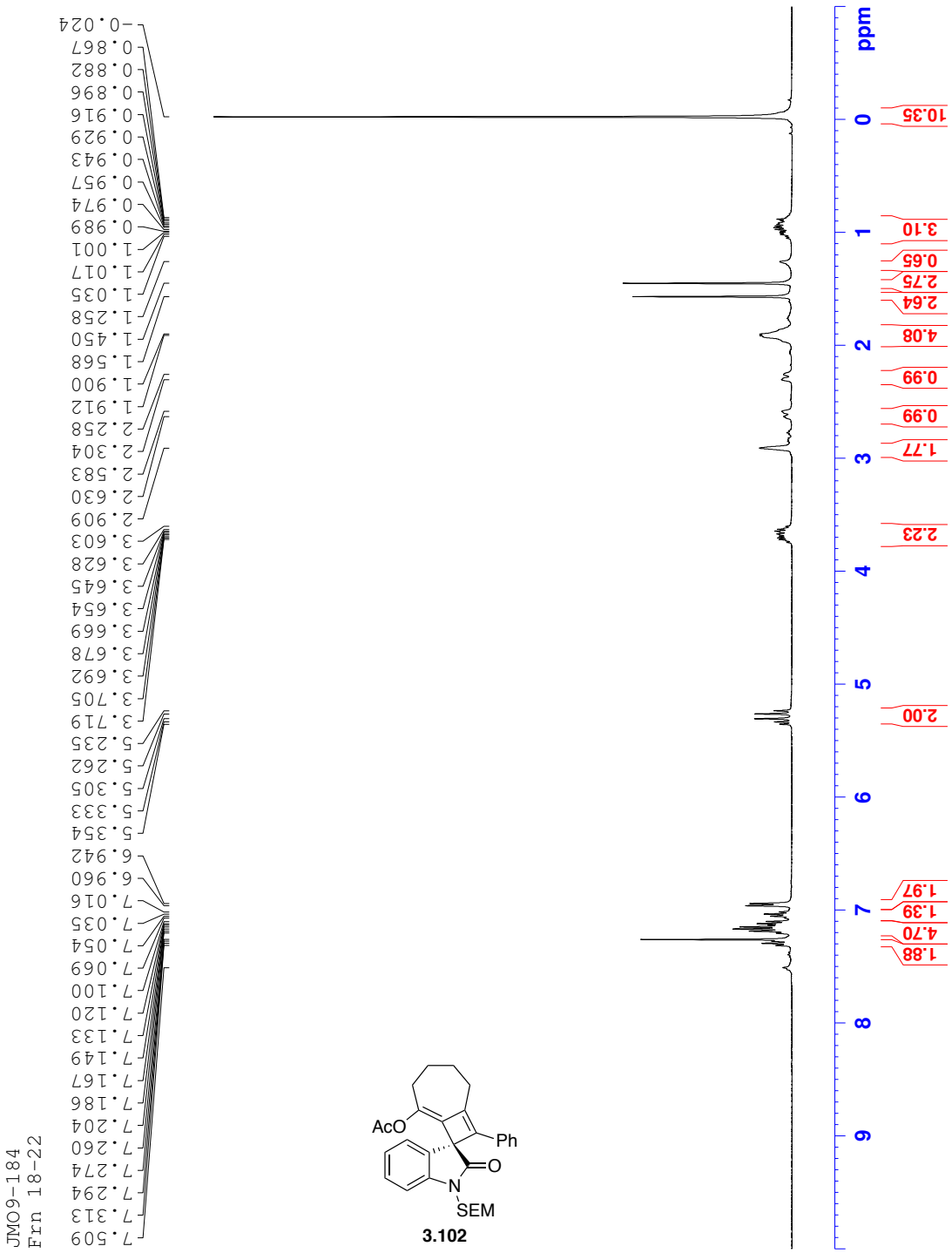
2.466
2.477
2.480
2.481
2.500
2.501
2.522
2.669
2.670
2.672
2.677
2.679
2.683
2.684
2.686
2.688
2.691
2.692
2.702
2.706
2.713
2.716
2.728
2.750
2.765
2.767
2.785
2.807
2.818
2.828
2.835
2.840
2.843
2.860
2.863
2.865
3.448
4.958
4.993
4.996
5.000
5.062
5.232
5.268
5.297
5.335
5.784
5.807
5.816
5.817
5.828
5.840
5.863
5.872
5.874
5.884
5.885
5.896
5.897
5.918
5.919
6.925
6.950
7.008
7.033
7.058
7.095
7.098
7.110
7.115
7.136
7.166
7.191
7.211
7.235
7.276
7.284
7.293
7.300
7.327
O
O
8
O
Ph
O
N
MOM
3.100
8.41
1.99
2.23
6.06
2.2
2.07
3.11
1.06
0.948
2.09
1
2
1.14
5.08
1.57
0
1
2
3
4
5
6
7
ppm 8


JMO9-184
Frn 18-22
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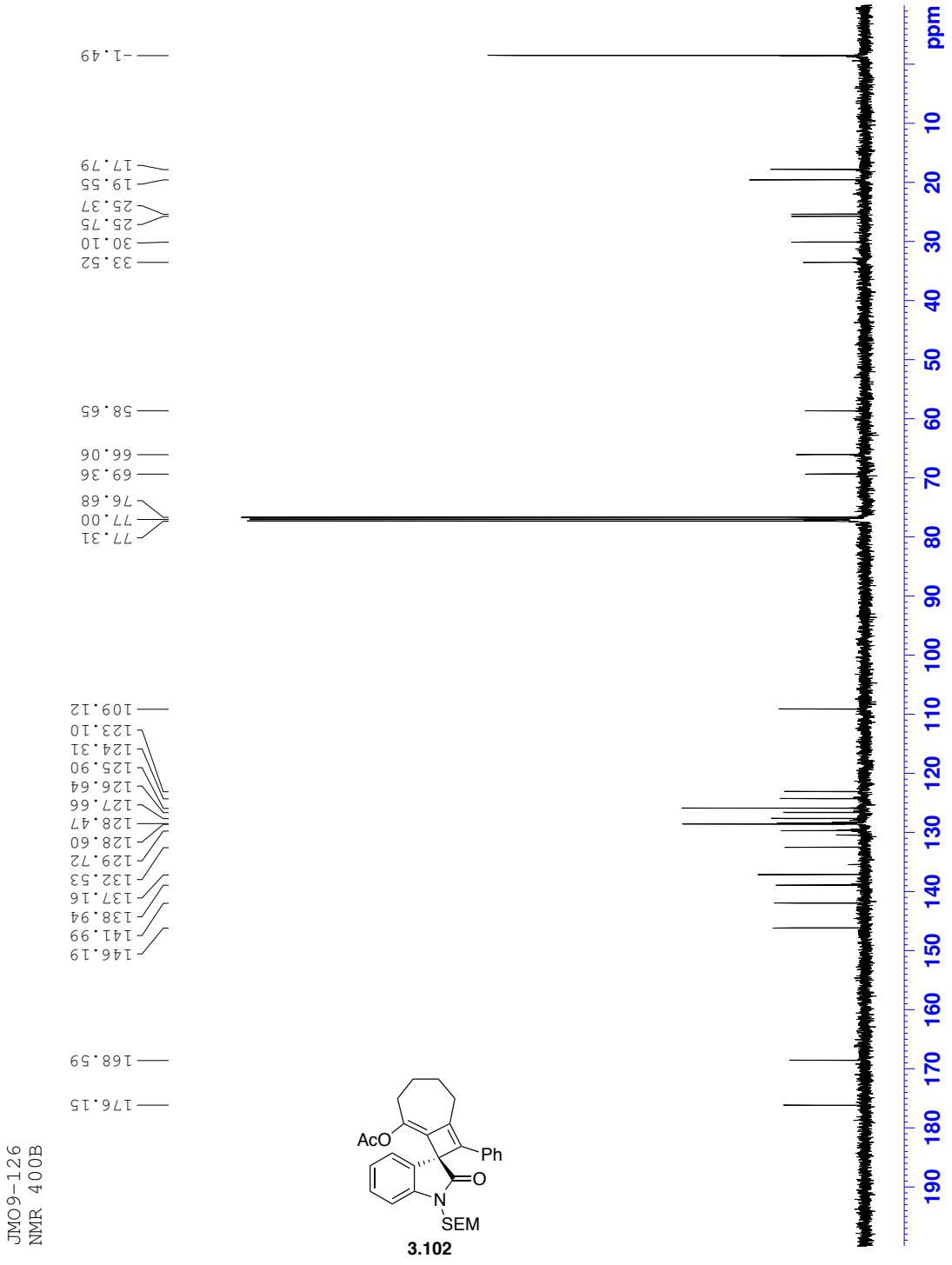
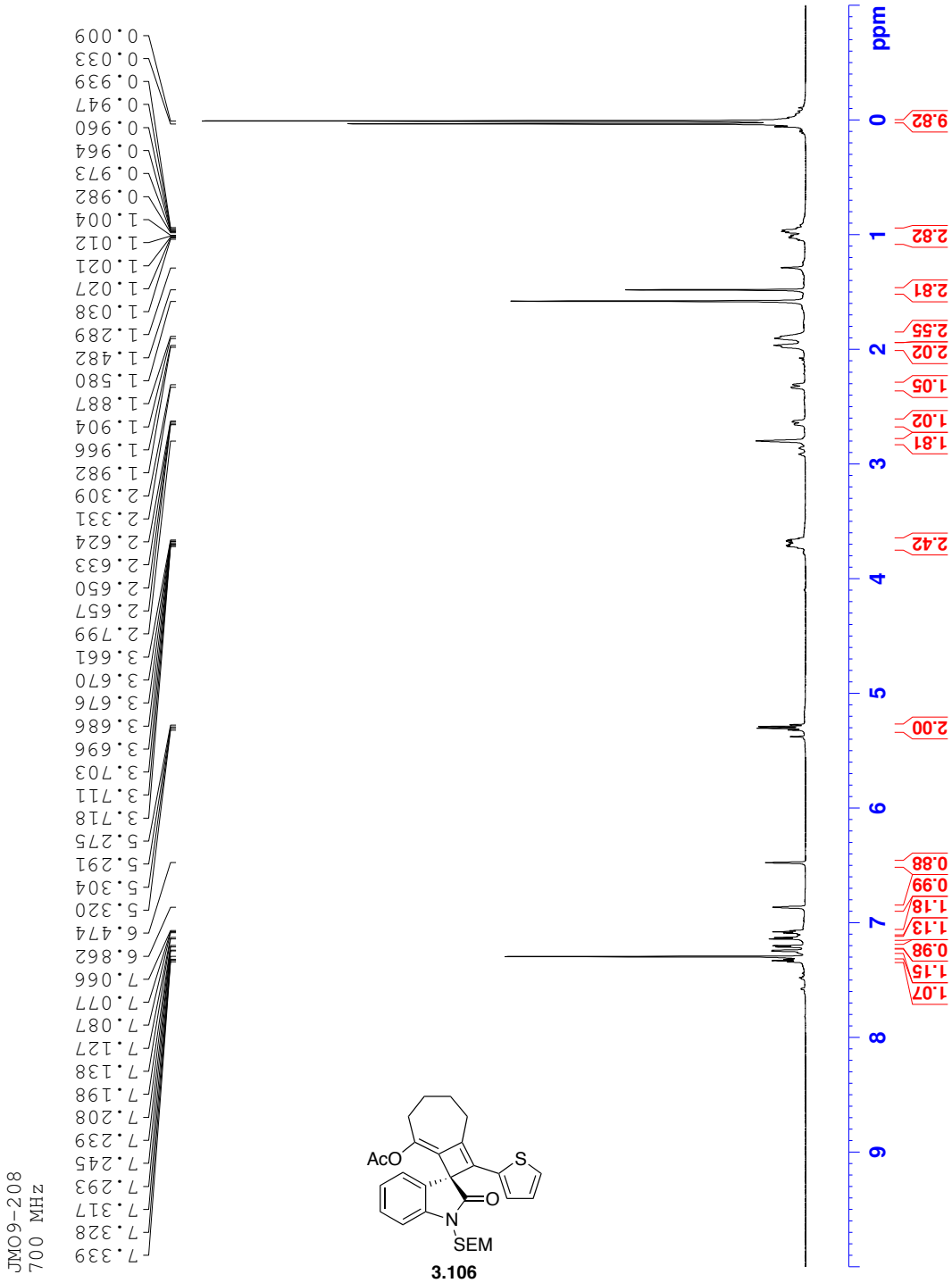
7.294
7.274
7.260
7.204
7.186
7.167
7.149
7.133
7.120
7.100
7.069
7.054
7.035
7.016
6.960
6.942
5.354
5.333
5.305
5.262
5.235
3.719
3.705
3.692
3.678
3.669
3.654
3.645
3.628
3.603
2.909
2.630
2.583
2.304
2.258
1.912
1.900
1.568
1.450
1.258
1.035
1.017
1.001
0.989
0.974
0.957
0.943
0.929
0.916
0.896
0.882
0.867
-0.024
ppm
0
1
2
3
4
5
6
7
8
9
10.35
3.10
0.65
2.75
2.64
4.08
0.99
0.99
1.77
2.23
2.00
1.97
1.39
4.70
1.88
AcO
Ph
O
N
SEM

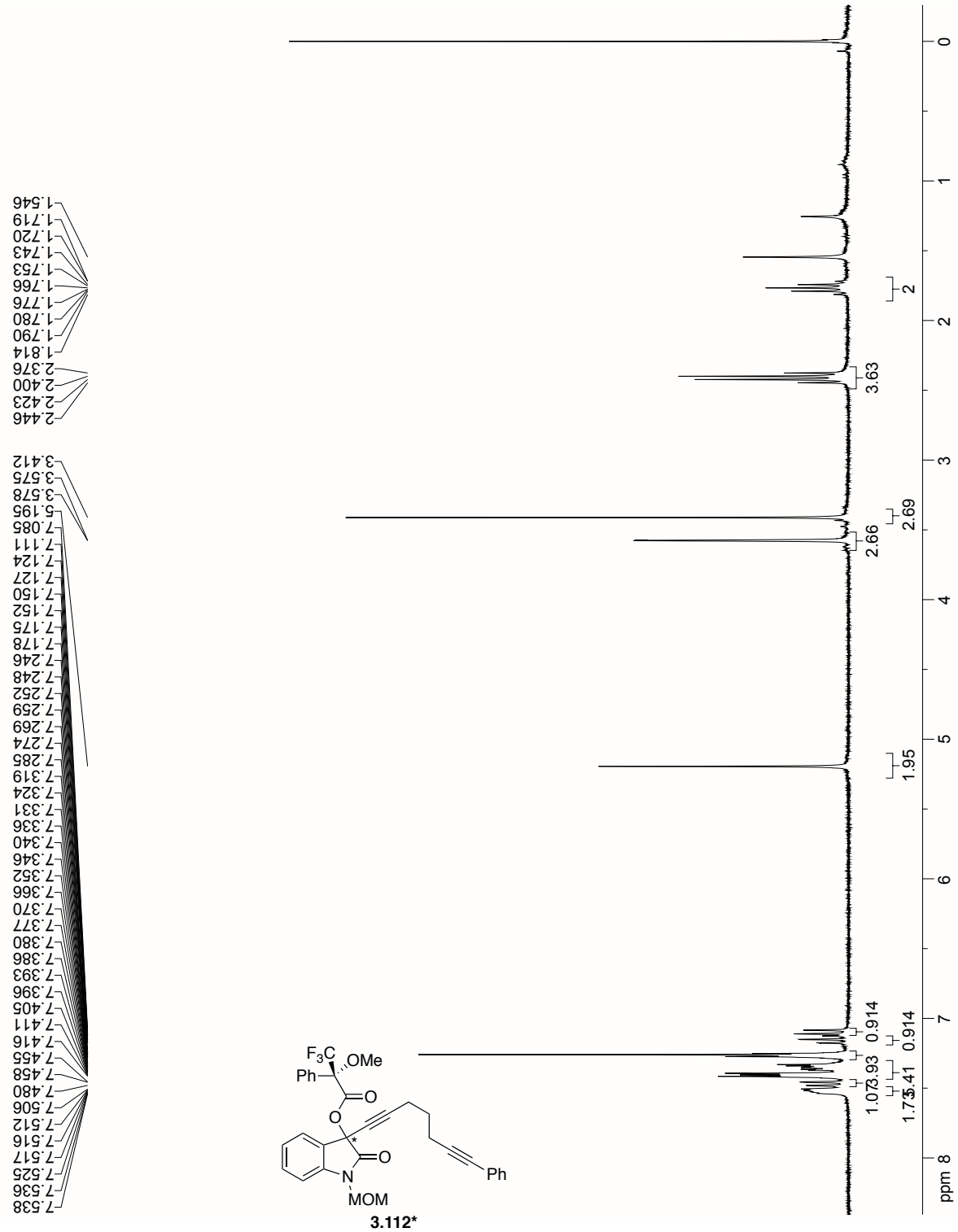
3.102

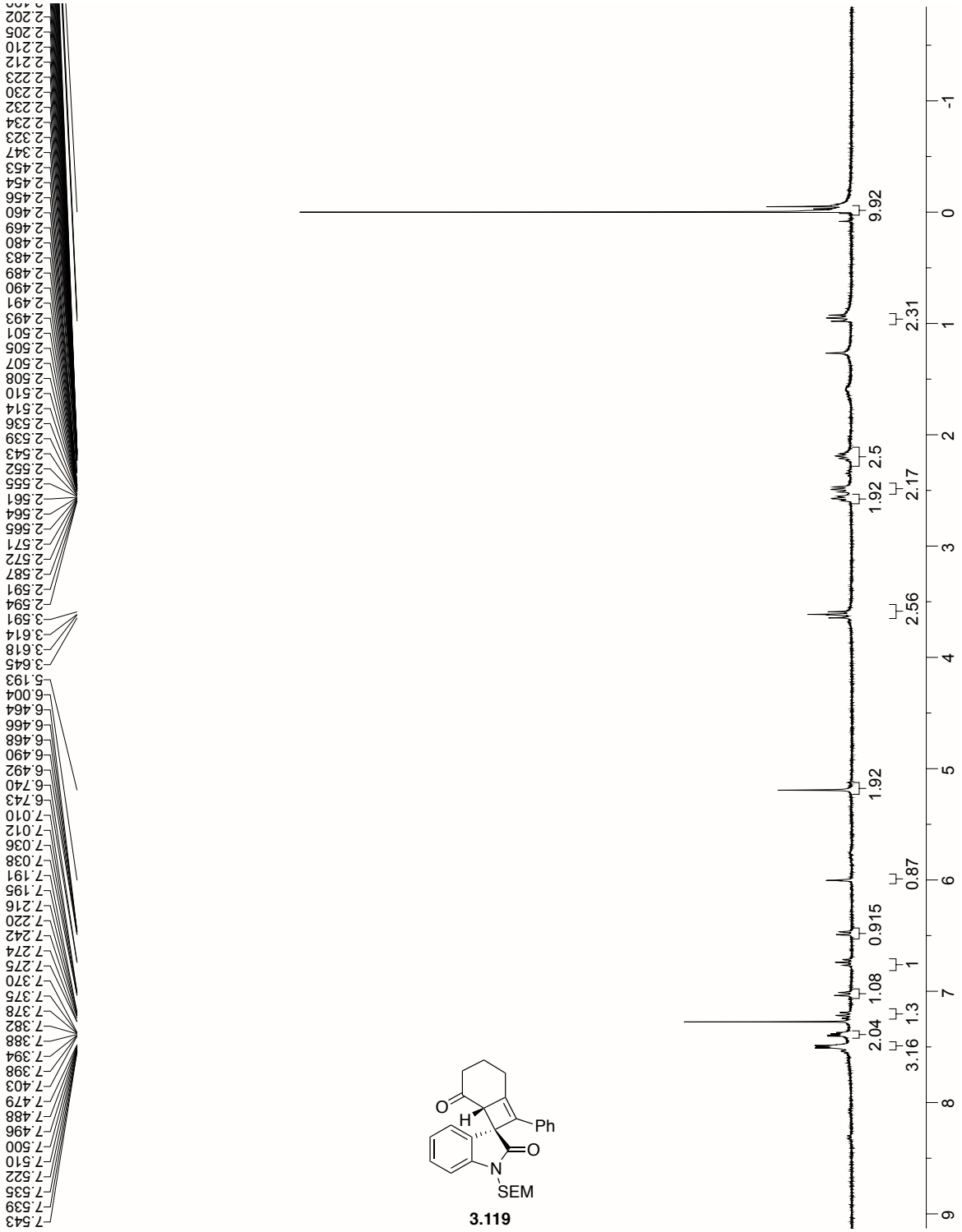

JMO9-126
NMR 400B
-1.49
17.79
19.55
25.37
25.75
30.10
33.52
58.65
66.06
69.36
76.68
77.00
77.31
109.12
123.10
124.31
125.90
126.64
127.66
128.47
128.60
129.72
132.53
137.16
138.94
141.99
146.19
168.59
176.15
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
AcO
Ph
O
N
SEM

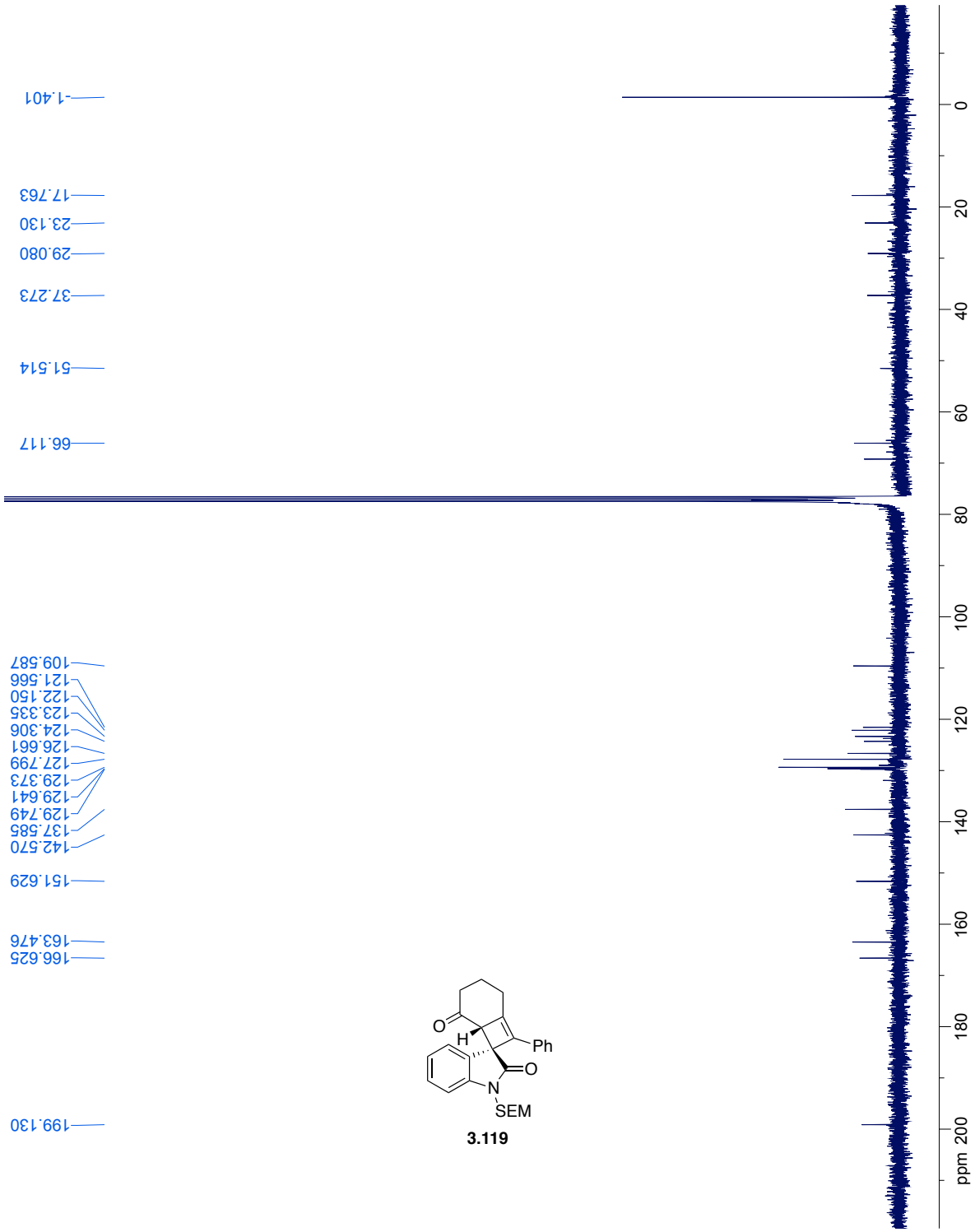
3.102


JMO9-208
700 MHz
AcO
S
O
N
SEM
3.106
ppm
9.82
2.82
2.81
2.55
2.02
1.05
1.02
1.81
2.42
2.00
0.88
0.99
1.18
1.13
0.98
1.15
1.07

JM09-208
700 MHz
175.73
168.68
143.60
142.27
137.33
135.12
133.60
129.71
128.75
127.51
126.54
126.00
124.53
124.36
123.13
109.20
76.94
69.48
66.07
33.66
29.46
25.65
25.55
19.63
17.88
0.01
-1.42
AcO
S
O
N
SEM
3.106
0 ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190


1.546
1.719
1.720
1.743
1.753
1.766
1.776
1.780
1.790
1.814
2.376
2.400
2.423
2.446
3.412
3.575
3.578
5.195
7.085
7.111
7.124
7.127
7.150
7.152
7.175
7.178
7.246
7.248
7.252
7.259
7.269
7.274
7.285
7.319
7.324
7.331
7.336
7.340
7.346
7.352
7.366
7.370
7.377
7.380
7.386
7.393
7.396
7.405
7.411
7.416
7.455
7.458
7.480
7.506
7.512
7.516
7.517
7.525
7.536
7.538
F3C
OMe
Ph
O
O
O
N
MOM
Ph
3.112*
0.914
0.914
3.93
5.41
1.07
1.75
3.63
2.66
2.69
1.95
2
ppm 8
7
6
5
4
3
2
1
0


O
H
Ph
O
N
SEM
3.119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17.763
23.130
29.080
37.273
51.514
66.117
109.587
121.566
122.150
123.335
124.306
126.661
127.799
129.373
129.641
129.749
137.585
142.570
151.629
163.476
166.625
199.130
ppm
0
20
40
60
80
100
120
140
160
180
200
O
H
Ph
O
N
SEM

3.119

2.167
2.176
2.186
2.466
2.476
2.485
2.549
2.551
2.557
2.559
2.566
2.568
5.154
5.998
6.000
6.002
6.463
6.464
6.465
6.475
6.476
6.721
6.722
6.732
6.733
6.743
6.744
6.988
6.999
7.191
7.193
7.202
7.204
7.213
7.215
7.367
7.368
7.370
7.372
7.373
7.378
7.381
7.416
7.422
7.426
7.475
7.480
7.482
7.486
7.490
7.493
O
H
Ph
O
N
MOM
3.123
2.33
3.36
1.21
1.52
1.08
1
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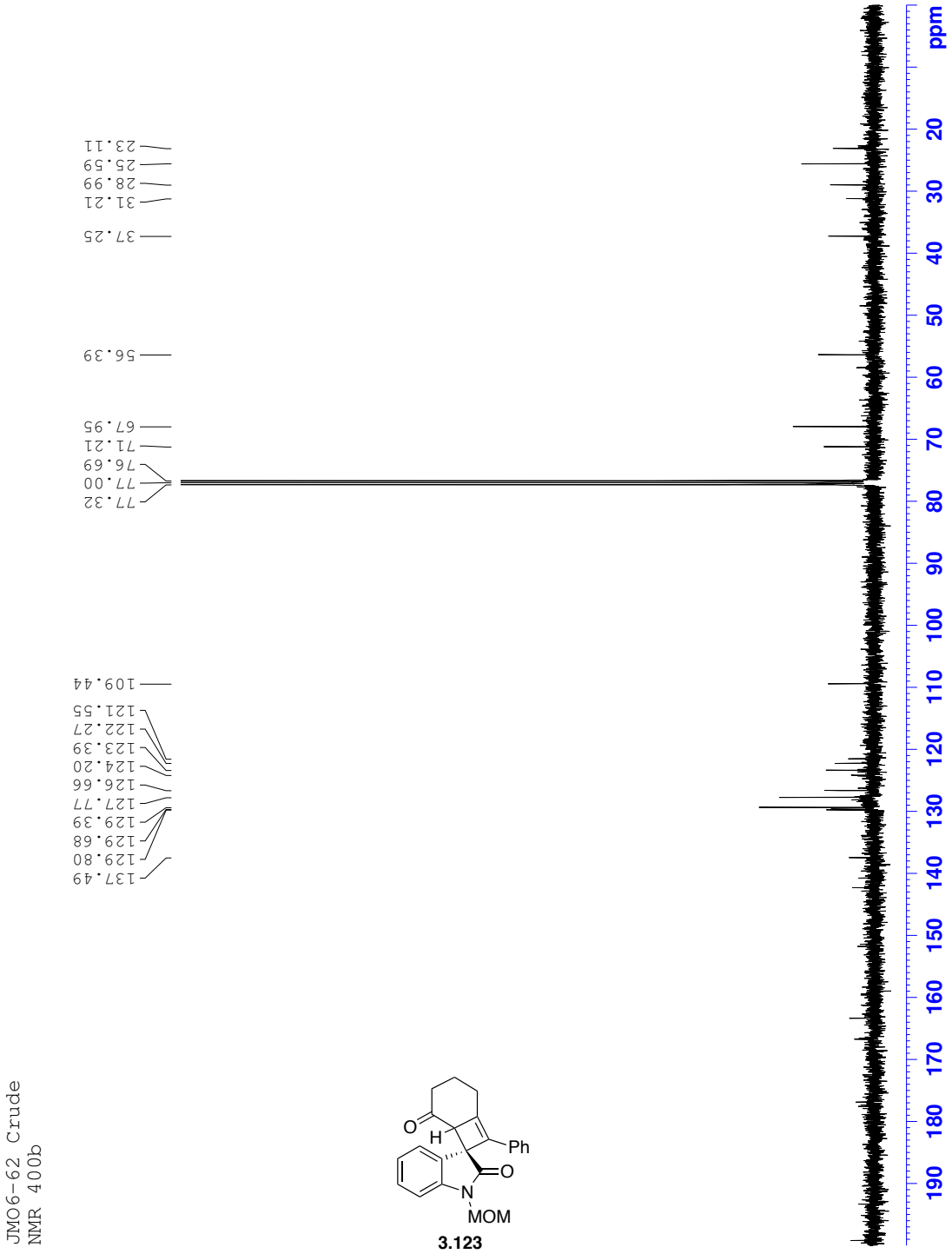
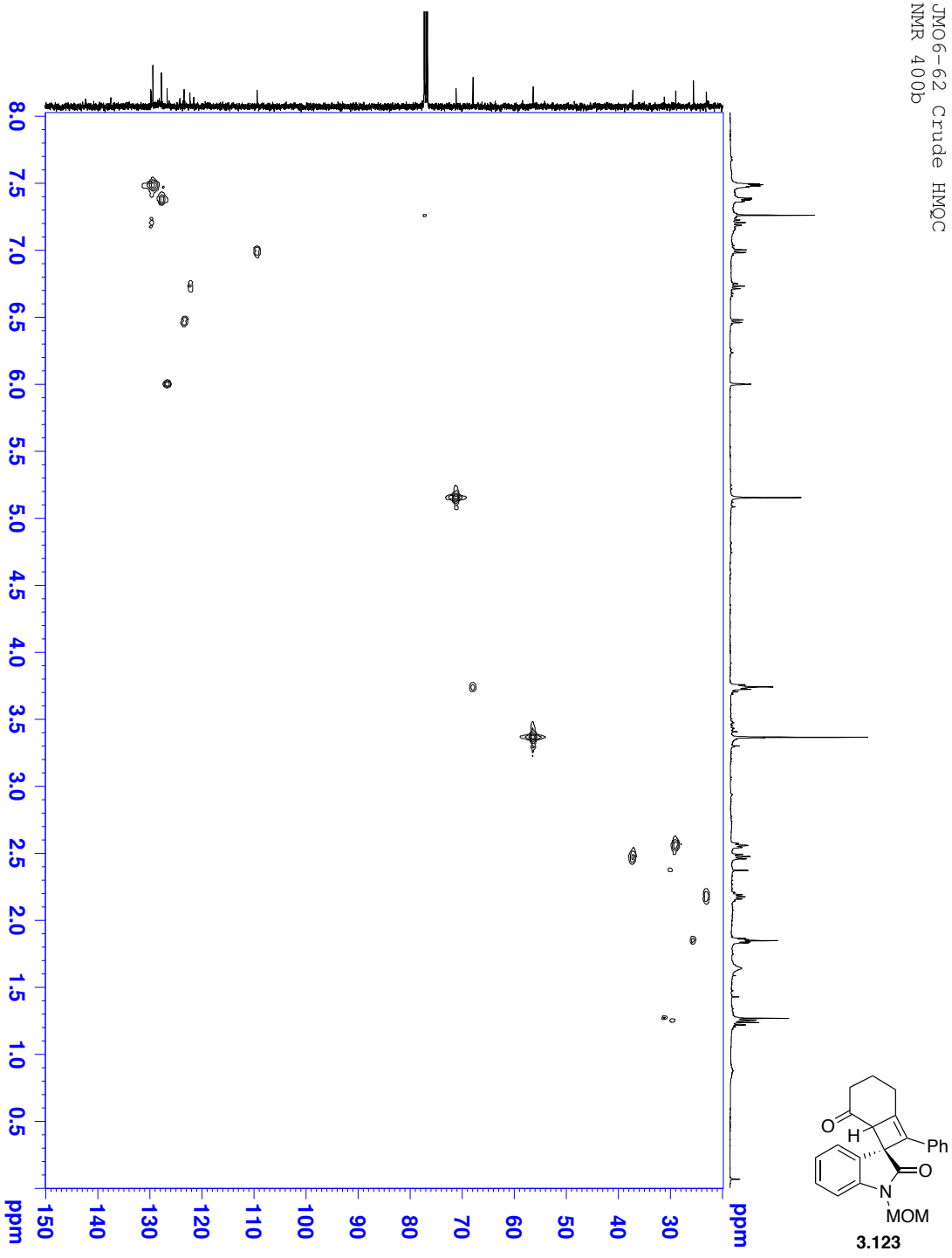
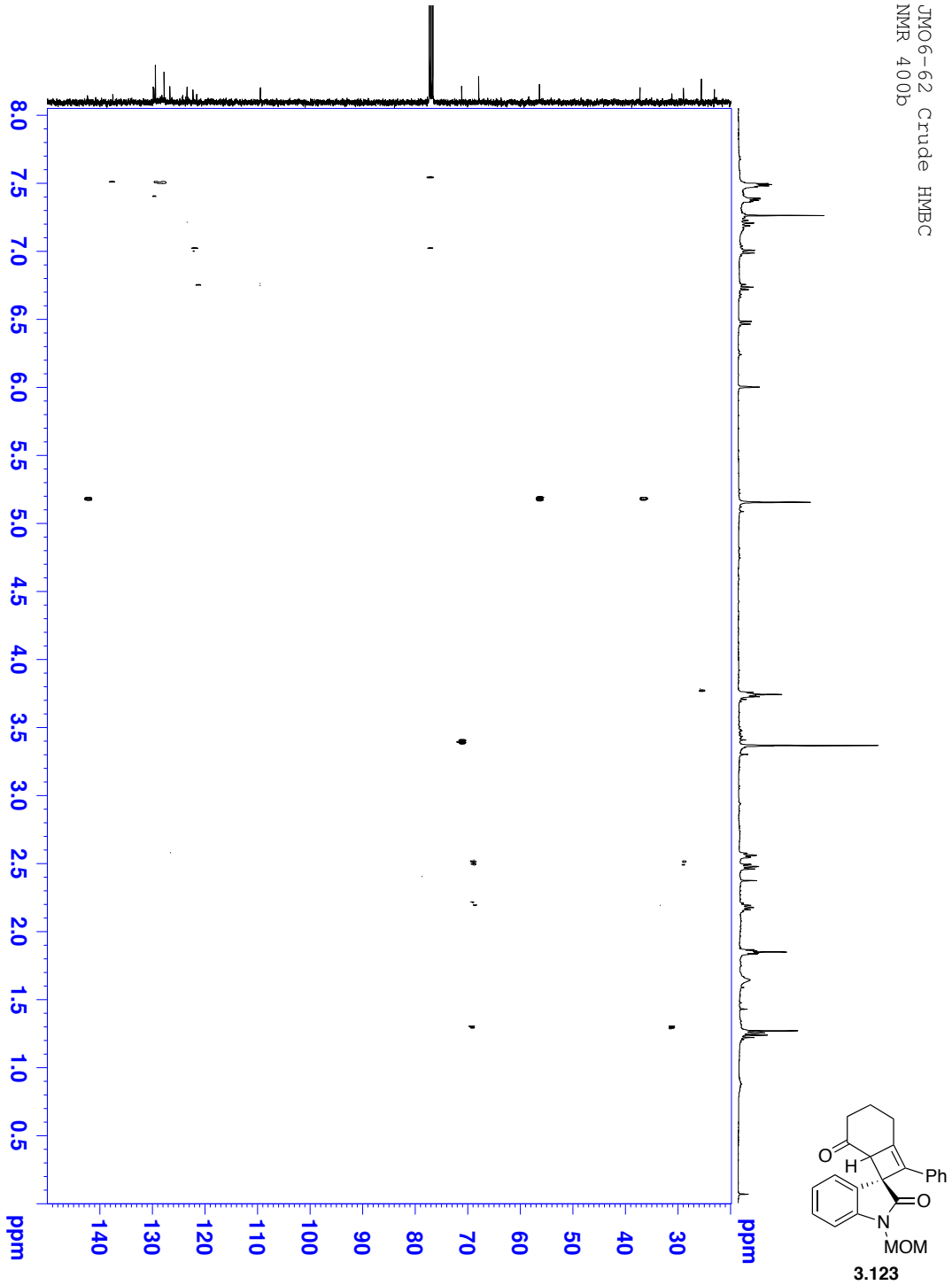
6
2.19
5
4
3.43
3
2.49
2.56
2.76
2
7
8


JMO6-62 Crude
NMR 400b
23.11
25.59
28.99
31.21
37.25
56.39
67.95
71.21
76.69
77.00
77.32
109.44
121.55
122.27
123.39
124.20
126.66
127.77
129.39
129.68
129.80
137.49
ppm
O
H
Ph
O
N
MOM

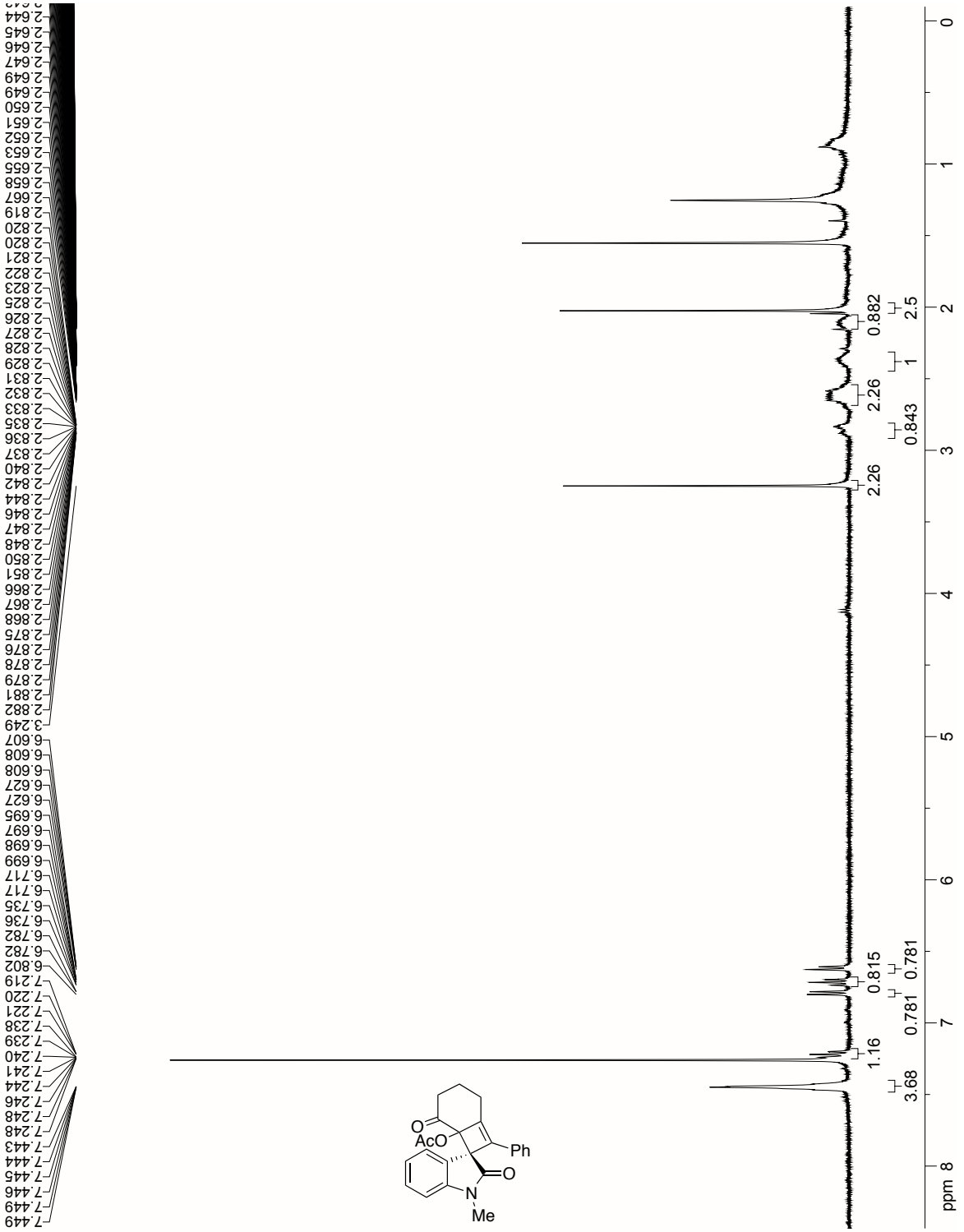
3.123



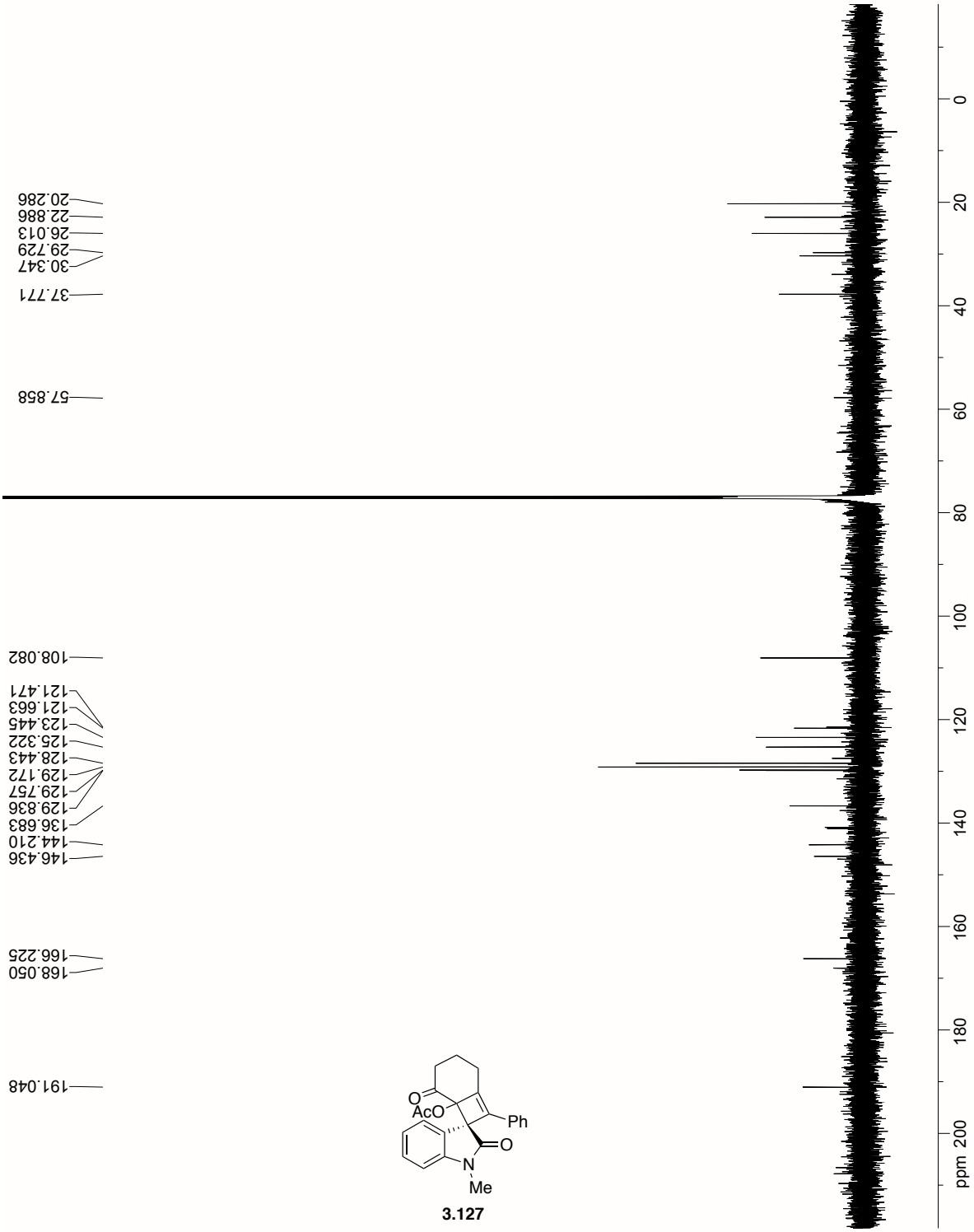
1J C-H HMQC Correlations



2J & 3J 1H-13C HMBC Correlations



3.127


20.286
22.886
26.013
29.729
30.347
37.771
57.858
108.082
121.471
121.663
123.445
125.322
128.443
129.172
129.757
129.836
136.683
144.210
146.436
166.225
168.050
191.048
O
AcO
Ph
O
N
Me
3.127
0
20
40
60
80
100
120
140
160
180
ppm 200

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1. Alcaide, B.; Almendros, P.; Aragoncillo, C., Exploiting [2+2] Cycloaddition Chemistry: Achievements with Allenes. *Chem. Soc. Rev* **2010,** *39*, 783.

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